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SYMPOSIUM ON TUMORS

INVASION OF THE BONY PELVIS BY CARCINOMA OF THE CERVIX UTERI AS A CAUSE OF PATHOLOGIC CENTRAL DISLOCATION OF THE HIP

J. R. Elder, M.B., Ch.B., and N. M. Matheson, F.R.C.S.

London, England

FROM THE CENTRAL MIDDLESEX COUNTY HOSPITAL, LONDON, ENGLAND

In a Hunterian Lecture, in 1923, C. A. Joll stressed the fact that squamous cell tumors have a strong tendency to give rise to secondary growths in the skeleton, and, in support of this contention, quoted examples in which the primary neoplasm was in the uterus, tongue, esophagus, soft palate and penis. Carcinoma of the cervix uteri gives rise to metastatic deposits in bone less often than tumors of the corpus, which, according to Ewing, Willis, and other authors, form distant metastases in 5 per cent, or more, of fatal cases. Turner and Jaffe (1940) found eight cases with skeletal metastases in a series of 99 patients with cervical growths, but this must be regarded as an unusually high number. In postmortem reports on large series of cases, such as those compiled by MacCormack (1909), and Albers-Schönberg (1893), skeletal deposits are estimated to occur in less than one per cent. We have not ourselves observed a case. As a source of skeletal metastases carcinoma of the cervix uteri may be regarded as of minor importance.

During recent years, the invasive powers of cancer in closed cavities have received special emphasis. These are well demonstrated by the tumors at the thoracic inlet, first described by Pancoast, which, by involving the structures at the root of the neck in a neoplastic mass, give rise to the syndrome which bears his name. A striking and constant roentgenologic feature of these growths is that they invade the upper ribs and occasionally the vertebral column. The object of the present communication is to draw attention to the effects of similar direct invasion of the pelvis in the late course of carcinoma of the cervix, of which little notice has been taken hitherto. This local destruction is not of uncommon occurrence, and its consequences may contribute largely to the clinical picture.

It has been stated by Warren, Harris and Graves (1936) that carcinoma of the prostate invades the bones of the pelvis by extension along the perineural lymphatics, and Meigs and Jaffe (1939), and Auster and Sala (1940), have argued that carcinoma of the cervix may reach them in the same way. The experiments of Batson (1940) have shown, beyond doubt, that carcinoma of the prostate is distributed to the bones of the spine and pelvis by the venous system. It seems, equally beyond doubt, that carcinoma of the cervix attacks the pelvic wall as the final stage in a continuous lateral spread. Victor Bonney has repeatedly stressed the importance of the nodes high up in the obturator fossa, in the lymphatic spread of carcinoma of the cervix, and it is in their neighborhood that skeletal invasion by direct extension begins and reaches its maximum. The mass of nodes, when it attains large size, may be felt *per vaginam*, and its outline may, occasionally, be seen in roentgenograms. The region of the acetabulum is most usually affected, but local extension in other directions may destroy other portions of the pelvis.

In the ultimate stage, also, pathologic dislocation of the hip, or *protrusio acetabuli*, may take place, and this, in our experience, is the most common cause of this rather rare event. The fact that it may occur in this way is insufficiently recognized. Illingworth and Dick (1941), for example, state that pathologic dislocation of the hip is always of the dorsal variety, while Watson-Jones (1940) makes no mention of malignant disease as a factor in its production. Vacchelli, quoted by Watson-Jones (1926), records the occurrence of central dislocation in tuberculous disease of the hip, but we have not found mention of it in the present connection. In the cases of which notes are appended, central dislocation due to destruction of bone in the region of the acetabulum is shown at various stages of its development. It is perhaps relevant to note that over the considerable period in which these cases were observed the only instance of traumatic dislocation of the hip, of any variety, that came to our notice was of central dislocation in association with *fragilitas ossium*.

Pain in these cases is often extremely severe, and appears to be due to implication of the sacrococcygeal plexus or the obturator nerve in the malignant process, though in advanced cases the lesion in the bone must make a large contribution. While it must be admitted that the grossest degrees of bony destruction are not very frequently seen, it seems equally true that this is only because so many patients die from sepsis, hemorrhage or uremia before these lesions have had time to develop, and that routine roentgenologic examination of the pelvis in cases of inoperable carcinoma of the cervix would reveal it in its earlier stages much more frequently than is appreciated.

CASE REPORTS

Case 1.—The patient was 47 years of age. Her illness began with vaginal bleeding two and one-half years before admission. She was treated with radium followed by total hysterectomy in June, 1933, and remained fairly well for a year. She then noticed several small lumps over the pubis, and had further radium treatment, which was re-

peated in October, 1934, and, again, in June, 1935. She fell and hurt her right hip, September 24, 1935, two days before her admission.

She was found to be in poor general condition. Several small masses were palpable above the pubes on each side of the midline. Movement at the right hip was slight, and extremely painful. She died eight days later.

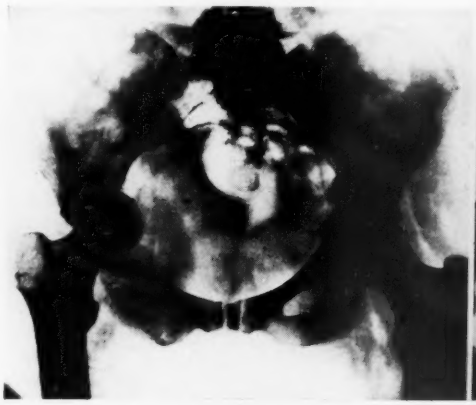

FIG. 1.—Case 1: Roentgenogram of pelvis, showing the outline of a neoplastic mass in relation to the right acetabulum, invasion of the adjacent bone, and central dislocation of the hip.

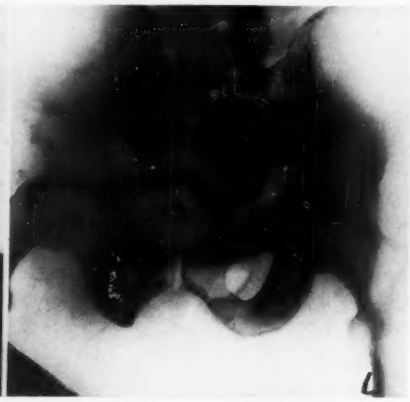

FIG. 2.—Case 2: Roentgenogram of pelvis, showing outline of neoplastic mass, decalcification in acetabular region, and impending central dislocation.

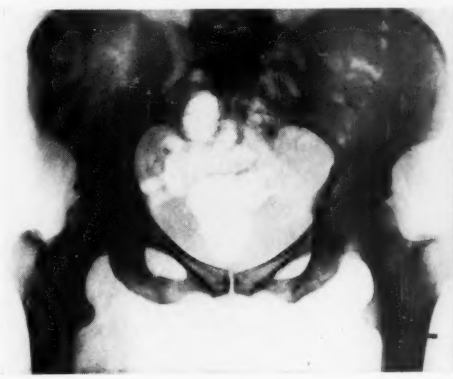

FIG. 3.—Case 3: Roentgenogram of pelvis, showing commencement of carcinomatous invasion.

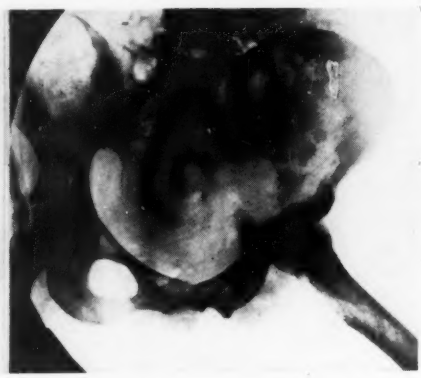

FIG. 4.—Case 3: Roentgenogram of pelvis, showing gross degree of destruction, with impending central dislocation of the left hip.

In the roentgenogram of the pelvis (Fig. 1) the outline of a neoplastic mass, in relation to the right acetabulum and obturator foramen, is clearly seen. There is decalcification and erosion of the bone in the region of the acetabulum and the ischium, with central dislocation of the femoral head.

Case 2.—The patient, age 61, was admitted, July 11, 1936, complaining of vaginal bleeding for nine months and urinary incontinence for three days. She had been in severe pain of a "bearing-down" character for a month. She was found to have an indurated ulcer replacing the cervix and involving the fornices and the vaginal walls, and infiltrating the tissues on the right side of the pelvis. Her pain became agonizing, with radiation along the distribution of the obturator nerve. She died, August 11, 1936.

In the roentgenogram (Fig. 2) the outline of the tumorous mass is again apparent. The right acetabular region is invaded, and decalfication has proceeded to a considerable

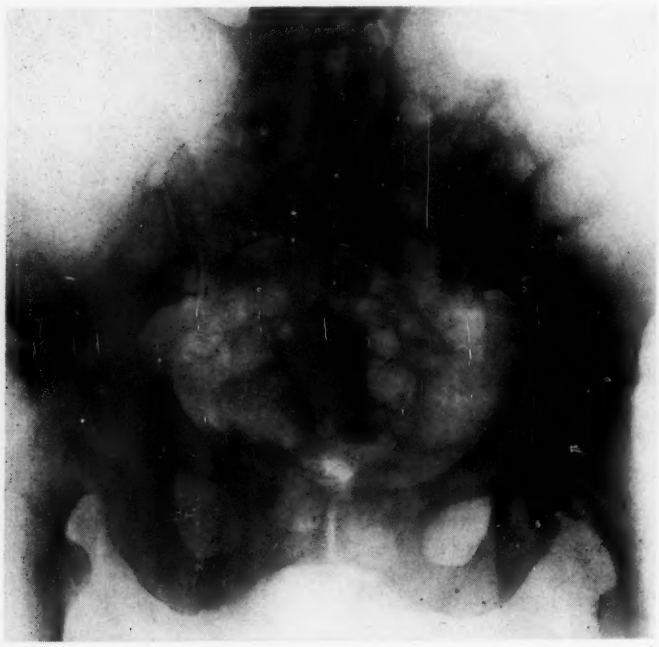

FIG. 5.—Case 4: Roentgenogram of pelvis, showing pathologic fracture in the region of the acetabulum.

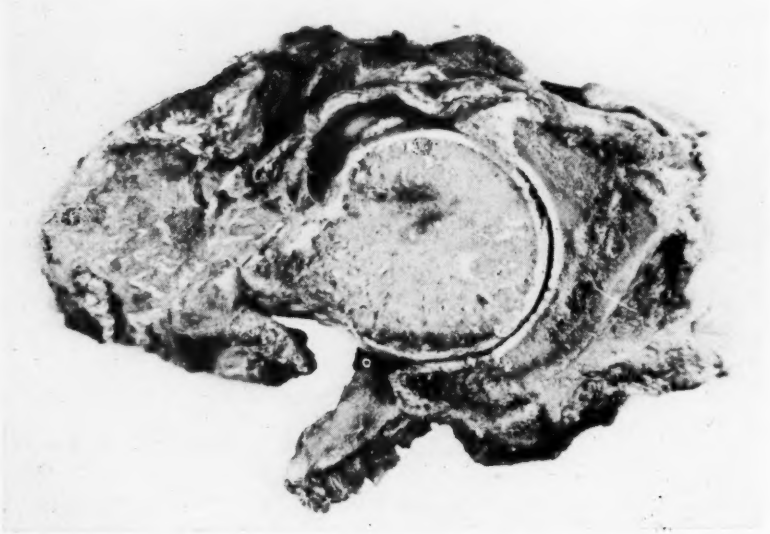

FIG. 6.—Case 4: Photograph of gross specimen obtained at autopsy showing tumor tissue invading the base of the acetabulum.

degree. It is evident that a comparatively small force applied to the trochanter would produce central dislocation of the femur.

Case 3.—The patient, age 39, was admitted, December 7, 1939, complaining of swelling of the left leg for six weeks. A carcinoma of the cervix was treated with radium in 1935, followed by three doses of deep roentgenotherapy. She had been well until the leg began to swell. No mass could be felt in the pelvis. One month later, the pain had become severe, commencing in the left sacrosciatic foramen and radiating to the foot. A tender, diffuse mass could be felt *per vaginam*, high on the left side. The cervix appeared healthy, and the uterus was small and mobile. A roentgenogram taken at this time (Fig. 3) shows commencing invasion of the ileum. Much relief was obtained by endothecal injection of alcohol, but for a short time only, and this was repeated on several occasions. The patient's condition gradually became worse, with steady enlargement of the neoplastic mass and progressive destruction of the pelvic wall. The pain in the leg was excruciating at times, and was relieved only by division of the spinothalamic tract and, finally, April 4, 1940, by partial chordotomy. The patient died, June 21, 1940.

The last roentgenograms of the pelvis, which it was possible to secure (Fig. 4), was taken five weeks before death, and shows a gross degree of destruction, with impending central dislocation. This actually took place three weeks later, when the patient turned in bed.

Case 4.—The patient, age 61, was admitted, February 7, 1941, complaining of pain in the back for six months. She had had deep roentgenotherapy for carcinoma of the cervix in October, 1940. There was a large neoplastic ulcer in the region of the cervix, with palpable extension in the right side of the pelvis. She complained of severe pain in the right hip and leg from shortly after her admission until her death, which took place June 17, 1941. No injury had occurred.

A roentgenogram (Fig. 5), obtained postmortem, shows a pathologic fracture in the region of the acetabulum. The opacity in the lumbar vertebrae is not a metastasis.

At autopsy, tumor tissue was found to infiltrate the whole inner membrane of the pelvis, especially on the right side, and to involve the region of the right acetabulum, where the bone (Fig. 6) was infiltrated with whitish tumor tissue.

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UROLOGIC COMPLICATIONS OF CANCER OF THE RECTUM*

THOMAS F. MULLEN, M.D.,
AND
PAUL LESTROHAN, M.D.
SAN FRANCISCO, CALIF.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL, SAN FRANCISCO, CALIF.

A STUDY of the records of patients suffering from cancer of the rectum reveals an unusually high incidence of complications affecting the urinary system. While many of these become evident only after operation, they are frequently present before. It is difficult, however, to evaluate these preoperative urinary symptoms in many instances, because, in taking the history, there has been no definite attempt to elicit them. Kickham and Bruce[6] found that 30.4 per cent of males and 36.7 per cent of females, in the early operable group, had urinary symptoms while in late or inoperable instances of the disease, 60.7 per cent of males and 46.6 per cent of females had disturbances of urination. We have scrutinized the records of 93 patients in four different hospitals and find that 50 per cent of them presented symptoms of urinary difficulty upon admission. In a large number of the remaining 50 per cent, there was no record of interrogation in this regard. This group of 93 patients comprised 60 males and 33 females; the average age was 58, the youngest being 23 and the oldest 78. Thus, the greater part of them were in the age-group when such symptoms as nocturia, difficulty in urination, alterations in the urinary stream, pain and burning upon urination and other symptoms of cystitis are commonly present. A certain number of the males have latent obstruction at the neck of the bladder from various causes, the commonest of which is benign hypertrophy of the prostate and prostatitis. Engel[2] found this to be true in 5 per cent of 190 men operated upon at the Cleveland Clinic, and Fell[3] states that 12 out of 64 (18 per cent) of his group gave a prostatic history. In the group making up our study, the prostate was said to be enlarged in 29 per cent of those in whom the condition of the gland was noted, but in 50 per cent of the records the prostate was not mentioned, and the residual urine was estimated in only two. In the females, the condition of the anterior vaginal wall and the position of the bladder were not especially noted in 21 out of 33; in the remaining 12, marked cystocele and prolapse, causing pronounced difficulty in urination, was found in three.

More careful questioning and examination probably would have revealed a greater number of persons in this group who were potential candidates for urinary complications, if they actually were not having symptoms at the time. It seems that the discovery of such a serious disease as cancer of the rectum overshadows these other conditions, both in the mind of the patient and in

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the attention of the physician. In addition to these ordinary causes of urinary symptoms, the neoplasm of the rectum is, itself, a frequent cause, and with the advance of the disease the symptoms become more numerous and more marked. The close anatomic relationship of the bowel and the urinary passages, with the tendency to penetration of the coats of the bowel, increasing its permeability to a septic content and causing adherence of structures are factors in the etiology of these symptoms. There may be external pressure of a tumor, causing distortion of the ureter, bladder, or urethra, or variable degrees of narrowing up to actual obstruction. Ulcerating growths on the anterior wall of the lower half of the rectum are most liable to cause trouble. In Kickham and Bruce's[6] series there was evidence of extravesical pressure in 37.5 per cent, and actual bladder involvement in 25 per cent. In our study, since cystoscopy was undertaken in only two instances, we are unable to state the percentage of cases in which external pressure with distortion or obstruction was present. However, there was definite attachment to the bladder in four, the prostate in nine, urethra in one, and the vagina in three. The location of the neoplasm is shown in Table I.

TABLE I

LOCATION OF NEOPLASM

	No. of Cases
Upper rectum	48
Lower rectum	42
Not stated	3
Anterior wall	26
Posterior wall	17
Not stated	50
Attached to:	
Bladder	4
Prostate	9
Urethra	1
Vagina	3
Sacrum	1

Examination of the urine before operation revealed pus cells in 38 per cent. Red blood cells were present in variable amounts in 16 per cent, there was one instance of frank hematuria. Bacteria were present in 12, of these only one was cultured, a streptococcus being recovered.

TABLE II

URINE BEFORE OPERATION

White Blood Cells	
Under 10 to H. D. F.	57
Over 10 to H. D. F. (10 to loaded)	36
Red Blood Cells	
Present in	15
Bacteria	12
Cultures—streptococci	1

We feel that a more detailed history would have revealed an even higher incidence of urinary symptoms upon admission, and that examination of the

urinary tract with special emphasis on the detection of latent obstruction of the bladder neck should be undertaken in every case. Since symptoms of obstruction may later be due to operative nerve injury, it is desirable to have ruled out, and corrected, any other cause of obstruction in order to avoid confusion and misdirected treatment. The more frequent use of the cystoscope preoperatively, and routine urine cultures give information that helps to prevent the complications that occur after operation. The preoperative use of urinary antiseptics and irrigation of the bladder has the combined advantage of accustoming the urethra to the passage of a catheter and lessening the degree of infection. During the time of preparation for radical removal of the rectum, surgical correction of bladder-neck obstruction might be undertaken, and attention given to infected, sagging bladders in the female. The practicability of preliminary prostatic surgery is stressed by Kickham and Bruce,[6] who emphasize the fact that: "A previously compensated bladder in the presence of obstruction may be precipitated into complete retention by weakening of the detrusor" (by interference with vesicle innervation). Engel[2] also recommends relief of obstruction at the bladder neck first in patients who have dysuria and are approaching operation for cancer of the rectum.

TABLE III

PREOPERATIVE URINARY SYMPTOMS: 93 PATIENTS

No symptoms related to the urinary tract mentioned in the history in	47
Symptoms present in	46
Nocturia	21
Dysuria	13
Pain and frequency	10
Burning on urination	5
Difficulty starting stream	3
Slow starting stream	2
Small stream	2
Urgency	2
Discomfort in bladder	1
Hematuria	1

EXAMINATION

Prostate enlarged	9
Not enlarged	22
Not mentioned	29
Residual urine estimated in	2
Cystocele	3
Cystocele and prolapse noted as not present in	9
Not mentioned in	21
Cystoscopy	2
Blood chemistry	23
Renal function, dye excretion	60

Postoperative Complications.—The frequency of serious urinary difficulty after radical removal of the rectum has often been remarked, but is not generally appreciated. Hill, Barnes, and Courville[5] state that in answer to a questionaire sent out by them, 32 surgeons reported an instance of 50 per cent of vesical dysfunction following resection, 20 reported it in two-thirds,

or more, of their patients and seven reported its occurrence in 100 per cent of their cases. Kickham and Bruce quote Cattell as saying that over 75 per cent present such complications and Whipple[12] says that: "Frank urologic complications occurred in 50 per cent of his cases of radical resection." In the present study, the incidence was 64 per cent, complications occurring in 38 males and 18 females. The operations performed were of various types, and in 67 per cent spinal anesthesia was employed, the remainder being general, with one local.

TABLE IV

TYPE OF OPERATION

Operation in 87; no operation 5; radium 1	
Abdomino-perineal resection:	
1 stage	35
2 stages	9
Posterior resection—Kraske	7
Colostomy, posterior resection—Lockhart-Mummery	14
Hartman operation	2
Colostomy	15
Local excision	3
Perineo-abdominal resection	1
Resection and end-to-end anastomosis	1
Transfusions in	64

ANESTHESIA

Spinal	59
General	27
Local	1

Operations were performed by a number of surgeons—in four hospitals.

TABLE V

POSTOPERATIVE UROLOGIC COMPLICATIONS: 64 PER CENT
Males 38; Females 18

Retention	56 (64%)
Cystitis	28 (33%)
Pyuria	30 (35%)
Pain, burning, distress	17 (19%)
Dysuria	2
Hematuria	2
Epididymitis	2
Frequency	1
Anuria	1
Incontinence	1
Atonic bladder	1
Pyelonephritis	1
Edema of penis and scrotum	1
*Neurogenic bladder	1

*(Male, age 48. Adenoca. just inside anus. Abd: Per. Resect. 1 stage; Spinal anesth. Catheterized four months).

These complications following operation are due to one or all of four factors:

First, direct injury to the tract. This occurred in two instances in this group, one, an intentional partial resection of the urethra, the other, an unintentional injury to the urethra with subsequent perineal urinary fistula. Such accidents may be unavoidable in the difficult dissection that is sometimes

entailed, and the only precaution that can be taken is to identify the structures carefully. A great aid to this is the presence of a catheter in the urethra or the ureters, as the case may be, during operation. There is always considerable reaction in the base of the bladder and the urethra when close dissection is necessary; sections of the bladder wall show this in the form of ecchymosis, thrombosis of small vessels, and infiltration with inflammatory products after a few days.

Second, loss of the supports of the bladder in the destruction of the pelvic floor with postoperative sagging of the bladder into the large posterior dead space, which is always infected. This causes pooling of the urine in the hanging sac of the bladder which soon becomes infected in every case. Lerch quotes Hochenegg and Heyrovski, who showed direct extension of bacteria into the intact bladder after operation. Postoperative packing of the posterior wound will help to prevent this, but the pack must be left long enough to permit the bladder to become fixed. Unless the pack is held in place by some sutures it quickly falls out and prolapse of the bladder occurs.

Third, the necessity for postoperative catheterization, with the almost inevitable infection that follows. Fell[3] states that 25 to 30 per cent of patients will void spontaneously; in this group, 32 per cent voided normally in the first 24 hours, 68 per cent were catheterized, intermittently in 27 per cent and by a retention catheter in 41 per cent.

TABLE VI

INCIDENCE OF CATHETERIZATION—68 PER CENT

Voided normally in first 24 hours	27 (32%)
Intermittent catheterization in	24 (27%)
Duration:	
Average	10 days
Longest	32 days
Retention catheter in	36 (41%)
Duration:	
Average	15 days
Longest	120 days

In one hospital, it is routine procedure to place a retention catheter in all cases, so that in all of their patients retention must be said to have occurred. In four or five days the catheter is removed and the patient is stimulated to try to void, if unsuccessful the catheter is replaced. In another hospital, intermittent catheterization was employed twice as often as was a retention catheter, and in the two other hospitals the two methods were employed about equally. It is to be remarked that postoperative orders in regard to catheterization were very variable, and in only one of the institutions were there definite and specific orders as to who was to catheterize, and as to when, and how it was to be done. Such orders as: "If unable to void catheterize," "If distended catheterize," or "If in pain catheterize" were noted, and indicate a lack of appreciation of the damage that can be done to the bladder by overdistention and infection. This has been shown by Munro and Hahn[8] in their study on tidal drainage.

TABLE VII

Hospital	No. of Cases	Voided, 24 hrs.	Retention Catheter	Intermittent Catheter	Cystitis	Pyuria
A	25	2	23	0	14	19
B	24	10	7	7	5	4
C	25	11	5	9	5	5
D	13	5	3	5	4	2

In hospital A, there were frequent examinations of the urine after operation, in the other hospitals, there were a large number in which this was not done; so that the incidence of pyuria and cystitis is undoubtedly higher.

TABLE VIII

URINE AFTER OPERATION

No record of examination..... 47
White blood cells
Less than 10 to H. P. F..... 11
More than 10 to H. P. F..... 35
(40-50-100-loaded)
Red blood cells..... 28
Bacteria..... 19
Cultures..... 6
Streptococci; *B. coli;* rods and chains; gram-negative rods; cocci
One man catheterized 34 days had but one urinalysis. Another for 14 days, until death, had one examination.

It is needless to say that every time a catheter is passed, especially into a damaged bladder, the possibility of infection again presents itself, and the indwelling catheter should be employed only with continuous tidal drainage, with occasional periods of rest for the urethra. Dukes[1] showed that pyuria appeared punctually in six to eight days in all women, and in 14 men, in whom a retention catheter was employed without tidal drainage. In the majority, this lasted for several weeks and in some for months. Two or three days before pus appeared, staphylococci were recovered in pure culture and a little later cultures showed mixed growths of *B. coli* and staphylococci. His cases were studied by daily microscopic examination of the urine and frequent cultures, in order to answer the question: "Has the patient escaped urinary infection?" It is remarkable that in so large a number of the cases studied by us (47 out of 87), there was no record of uranalysis after operation. Whipple[12] says that if adequate investigation of the urine were carried out in all cases, the incidence of cystitis after operation would be found to be 100 per cent.

Dukes uses a form for the recording of the incidence of pus cells as follows:

100,000	Pus 2 plus
10,000	
1,000	Pus 1 plus
100	Pus
10	Excessive leukocytes
0	Normal

The comparative merits of retention and intermittent catheterization has caused some debate. Many authorities place an indwelling catheter in the

bladder before or at the end of the operation, and leave it in for from four to five days to two weeks. After this period, intermittent catheterization is persisted in until there is no longer any residual urine. Fell[3] says that T. E. Jones has given up the use of a retention catheter and thinks that it is best to catheterize three or four times a day, having found that this plan leads to fewer complications. David also prefers intermittent catheterization, feeling that it causes less trauma to the urethra and is more comfortable for the patient.

Fourth, Injury to the Nerve Supply of the Bladder.—Why, out of a series of cases having the same type of operation, some will develop serious vesical

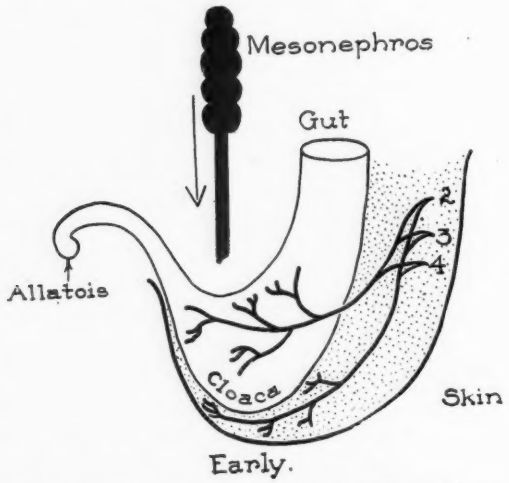


FIG. 1.—The cloaca and its nerve supply. (Redrawn from "A Method of Anatomy"[6] by J. C. Boileau Grant. Williams and Wilkins Co., Publishers.)

disability and others will escape, has been an intriguing question. It must be a question of anatomy, probably of fascial barriers and cleavage planes.

Grant,[4] in his Method of Anatomy, says that in lower forms the cloaca opens onto the skin surface through an opening guarded by a sphincter of striated muscle. In man, a septum of mesoderm, the urorectal septum divides the cloaca into an anterior and a posterior part; this also occurs to the cloacal sphincter, the anterior part becoming the transversus perinei, bulbospongiosus, ischiocavernosus, and the urogenital diaphragm, the posterior part becoming the sphincter ani externus. For these reasons, one nerve, the pudendal, a mixed nerve, supplies all of the muscles into which the cloacal sphincter divides as well as the skin about the orifice. The bladder and the rectum, for this reason, have a common nerve supply also, consisting of the pelvic splanchnic, which is parasympathetic, and most important, the hypogastric plexus, which is sympathetic, and the pudendal which is somatic. The pelvic splanchnic and the pudendal both arise from the second, third, and fourth

sacral segments; the pudendal is a mixed nerve which supplies voluntary muscle including the sphincter ani externus and the sphincter urethrae. The pelvic splanchnic, nervus erigens, is a mixed parasympathetic nerve; it supplies the involuntary muscles guarding the rectum and the bladder, the sphincter ani internus and the sphincter vesicae, as well as the detrusor muscle in the bladder wall. As it also supplies the arteries of the erectile

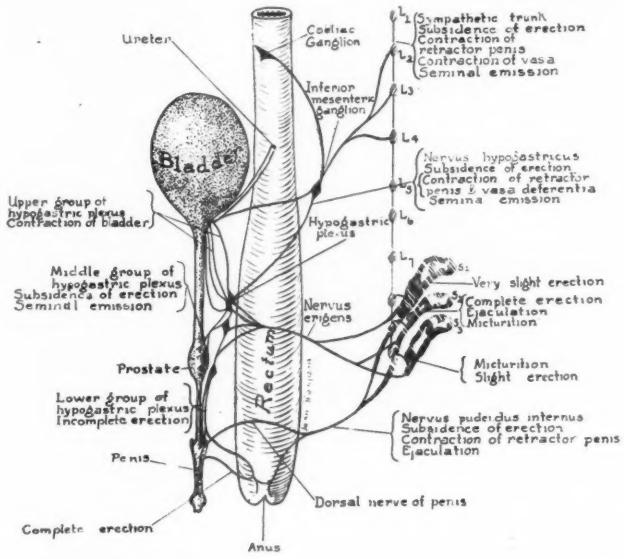


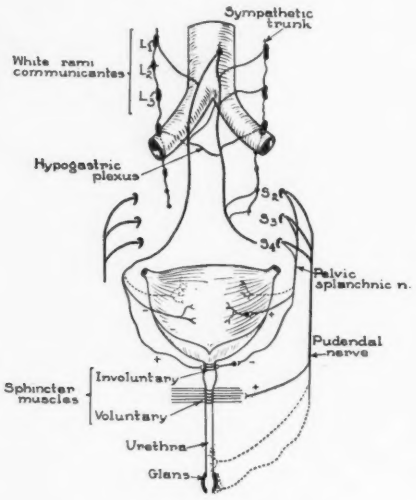
FIG. 2.—Pelvic nerve supply in the cat. (Redrawn from "Physiology of Micturition" by Langworthy, Kolb and Lewis.[7] Williams and Wilkins Co., Publishers.)

tissue of the penis and the clitoris, causing their relaxation and erection, it is called the nervus erigens. The afferent and the efferent fibers for the bladder are, therefore, in the paired pelvic splanchnic nerves, and for the urethra, in the paired pudendal nerves. The sympathetic fibers to the bladder travel by the mesenteric, hypogastric, and pelvic plexuses. The sympathetic trunk passes down on the bodies of the vertebrae behind the common iliac artery to reach the pelvis, branches pass from this trunk to the intermesenteric plexus, which extends down to become the hypogastric plexus or presacral nerve. This nerve lies below the bifurcation of the aorta, in front of the left common iliac vein and the promontory of the sacrum; on each side branches descend in front of the sacrum as the right and left pelvic plexus and are joined by branches of the pelvic splanchnic.

The relations of the pelvic splanchnic are of much greater importance in relation to the subject under discussion. Grant[4] says that they are most easily found by "passing two fingers down in front of the body of the sacrum and easing the rectum forward the fingers will occupy a little pouch which is bounded on each side by an areolar fold which contains the nervus erigens, and conducts it from the sacral foraminae to the side of the rectum." On

each side of the rectum, it joins the pelvic sympathetic of the same side and so becomes mixed sympathetic and parasympathetic. It forms a dense network, applied to the medial side of the vessels that limit the retropubic space posteriorly on each side, and is distributed to the pelvic viscera with these vessels. As it passes in from the parietes to the viscera, the nerve is in three parts, a proximal one, related to the bladder; a middle one, which supplies the urethra and the sex glands; and a third, or distal one, which enervates the bowel (Langworthy, Kolb, and Lewis,[7] who also say that the autonomic system is purely motor and passes in as distinct units, the parasympathetics always lying lateral to the sympathetics). Division or destruction of the parasympathetic fibers leads to an inability to empty the bladder, there is loss of normal tone and contraction, and the injury may be unilateral or bilateral. The bladder wall becomes hypertrophied and changes in the mucosa, due to infection, occur. Langworthy, Kolb, and Lewis believe that the sympathetic fibers have vasomotor and sexual functions in relation to the bladder and urethra, and that their activity is not necessary for normal micturition.

FIG. 3.



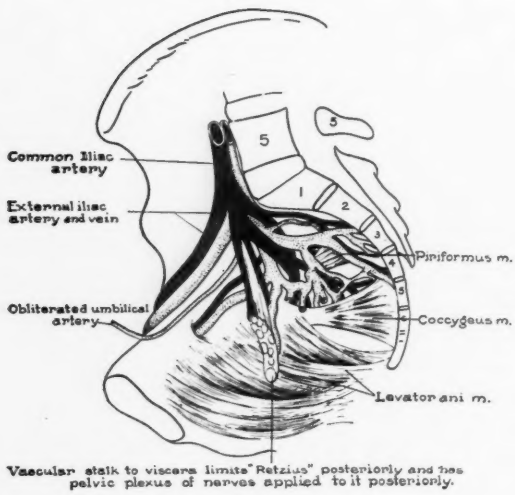


FIG. 4.

FIG. 3.—The nerve supply to the bladder and urethra. (Redrawn from "A Method of Anatomy" by J. C. Boileau Grant. Williams and Wilkins Co., Publishers.)

FIG. 4.—Redrawn from "A Method of Anatomy" by J. C. Boileau Grant. Williams and Wilkins Co., Publishers.

It would seem that the urinary dysfunction following excision of the rectum is usually due to injury to the parasympathetic nerve supply. It rarely occurs during the abdominal stage of the operation, and is rarely due to the encroachment of the tumor itself upon the nerve structures. It is

during the perineal or posterior resection that the injury usually occurs. It is at this stage that the pudendal nerve, also, is injured and, although it lies lateral to the usual line of incision, it may be injured by actual division or by traction. Its injury, or division, leads to incontinence, of which one instance occurred in this group. Mixed types of dysfunction can occur and are due to various degrees of injury to several of the nerve pathways.

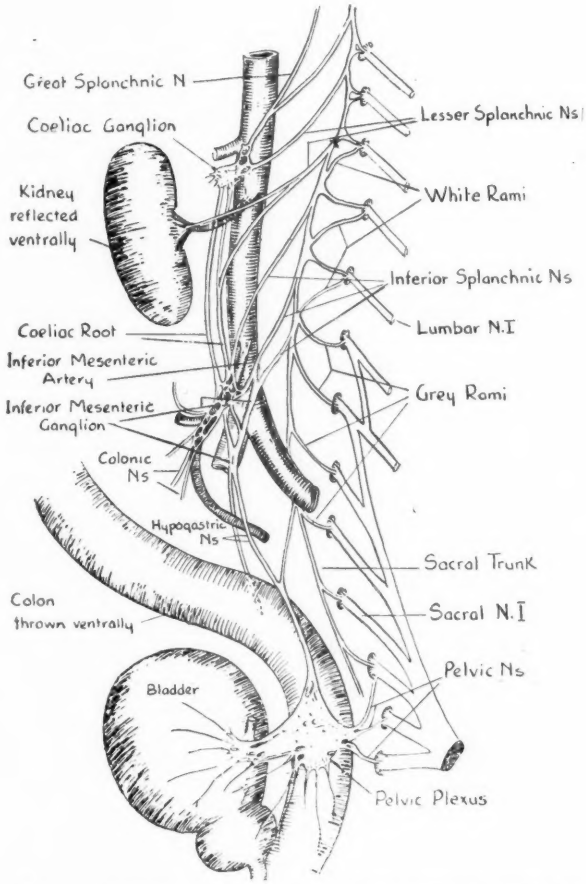


FIG. 5.—Arrangement of lumbar and sacral autonomic nerves in man (Trumble).

Descriptions of the pelvic fascia are difficult to understand, because it is not laid out in definite flat sheets, but covers the various pelvic viscera in diverging planes and angles. It is, however, probably due to a misconception of the distribution of the pelvic fascia that these injuries occur. There are four layers of fascia between the bladder and the rectum, according to Grant[4]: A layer clothing the base of the bladder; a layer clothing the front of the rectum; and the two other layers that clothe the seminal vesicles and the vas in front and behind. It is in the layers on the posterior wall of the pelvis

wound should be made and every attention given to the prevention of its infection.

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PAGET'S DISEASE OF THE NIPPLE

JOHN PETTIT WEST, M.D.
AND
WILLIAM F. NICKEL, JR., M.D.
NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY OF THE NEW YORK HOSPITAL, AND CORNELL UNIVERSITY MEDICAL COLLEGE NEW YORK, N. Y.

PAGET'S DISEASE of the nipple is not a common disease. Harrington,[1] in a review of 4,628 cases of carcinoma of the breasts, reports only 34 cases of Paget's disease, an incidence of 0.7 per cent. It is for this reason, perhaps, that the seriousness of an eczema of the nipple is not always appreciated.

In 1874, Sir James Paget[2] published an article titled: "On Disease of the Mammary Areola Preceding Cancer of the Mammary Gland." He stated that "certain chronic affections of the skin of the nipple and areola are very often succeeded by the formation of scirrhous carcinoma of the mammary gland."

His classical description of the clinical features of the disease, in the 15 patients he had observed, is in part as follows: "The disease began as an eruption on the nipple and areola. In the majority it had the appearance of a florid, intensely red, raw surface, very finely granular, as if very nearly the whole thickness of the epidermis were removed; like the surface of a very acute diffuse eczema. From such a surface, on the whole or greater part of the nipple and areola, there was always copious, clear, yellowish viscid exudation.

"It has happened in every case which I have been able to watch, cancer of the mammary gland has followed within, at the most, two years, and usually within one year. The formation of the cancer has not in any case taken place first in the diseased part of the skin. It has always been in the substance of the mammary gland, beneath or not far removed from the diseased skin, and always with a clear interval of apparently healthy tissue. In the cancers themselves, I have seen in these cases nothing peculiar. They have been various in form; some chronic, some acute, the majority following an average course, and all tending to the same end: recurring if removed, affecting lymph nodes and distant parts, showing nothing which might not be written in the ordinary history of cancer of the breast."

Because of the lack of a histopathologic description by Paget, there has been much confusion as to the true nature of the disease. Kilgore[3] states that to-day a definite histologic picture is recognized, consisting of "epithelial hypertrophy, subepithelial round cell infiltration and Paget's cells." Paget cells, so-called, are large edematous cells in the epithelium, vacuolated, and with shrunken pyknotic nuclei. Muir[4, 5] defines a Paget cell as a cancer cell growing within a healthy or at least nonneoplastic epithelium.

FIG. 1.

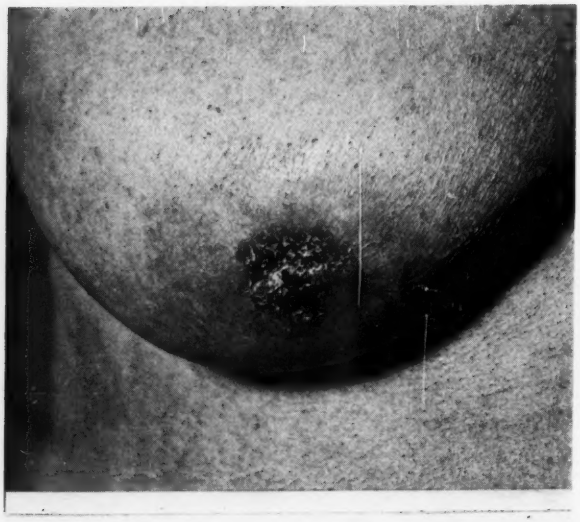

FIG. 2.

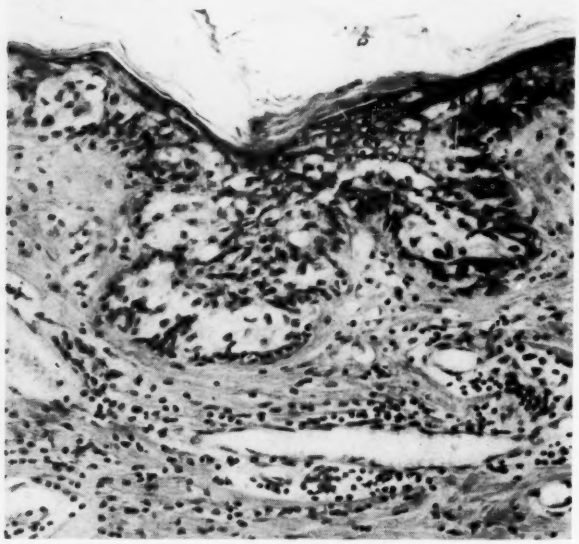

FIG. 1.—Case 1: Eczema of nipple and areola of two years' duration. Radical mastectomy. Nodes not involved. Well nine years.

FIG. 2.—Case 1: Section through nipple. Many Paget-cells are seen in the epidermis. (×275)

According to Caylor[6] there are at the present four chief opinions regarding Paget's disease: (1) That it is a dermatitis or eczema of the skin; (2) that it is a primary squamous cell epithelioma of the skin; (3) that it is a carcinoma developing from the lactiferous ducts in the nipple and the suderiferous ducts of the skin, secondarily involving the skin and breast tissue; and (4) that it is a carcinoma beginning deep in the breast and growing up along the ducts of the nipple and finally invading the skin.

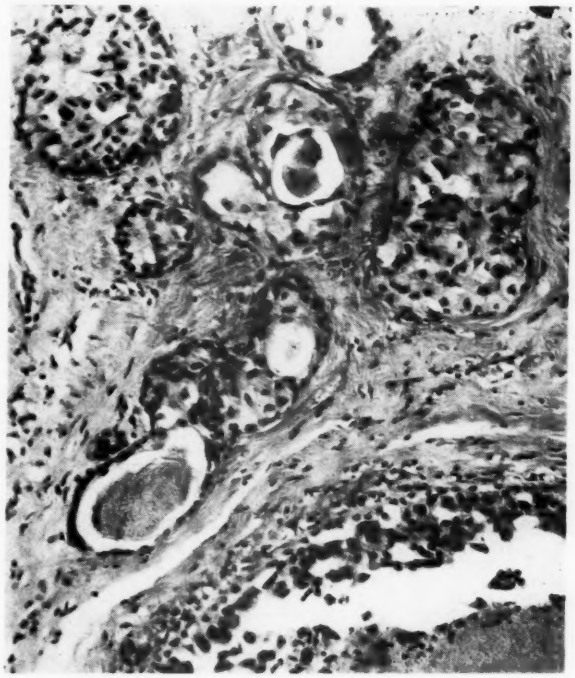

FIG. 3.—Case 1: Section through breast showing intraduct carcinoma. (×240)

Cheatle[7, 8] feels that the classic signs that Paget described are caused by more than one condition and that it is not correct to limit the diagnosis of Paget's disease of the nipple to those states in which "Paget cells" are present.

Muir believes that Paget's disease occurs only when intraduct carcinoma is present in the supper portions of the ducts in the nipple, and is due to the spread of the cancer cells from ducts to the epidermis by the intra-epithelial route.

Weiner[9] has published an excellent chronologic résumé of the more important literature on Paget's disease of the nipple. He was particularly interested in the extramammary form, and suggests that Paget's disease of the skin is the intra-epidermal metastasis from an underlying carcinoma of the apocrine sweat glands.

Ewing[10] states that "Paget's disease is a specific, chronic, progressive disease of the mammary nipple and adjoining skin, which is closely related

to, and almost invariably followed by, carcinoma. It is probably to be interpreted as a precancerous affection at first, limited to the epidermis and the gland ducts, but later becomes true carcinoma. The writer's conclusions regarding the nature of Paget's disease are influenced by clinical characters as well as histologic studies, which indicate that there are two clinical varieties. One finds a typical group of cases in which there is no definite tumor of the breast but a slowly progressive eczematous lesion affecting the epidermis about the nipple, not extending deeply into the ducts but spreading widely over

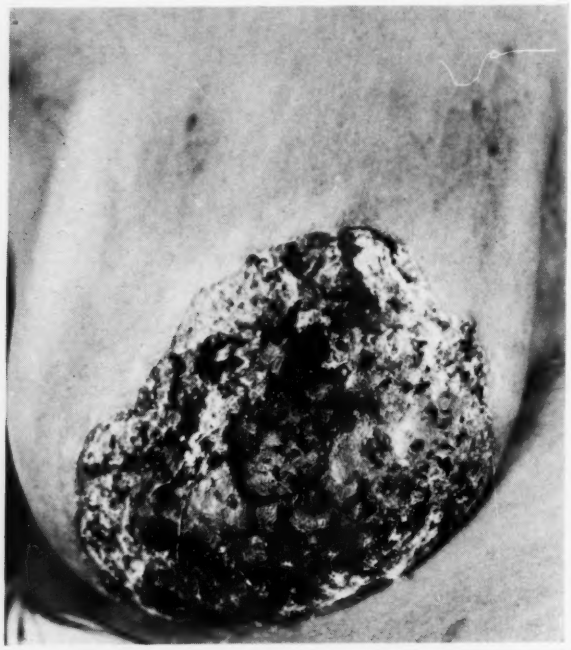

FIG. 4.—Case 2: Eczema of nipple and surrounding skin of one year's duration. Radical mastectomy. Nodes not involved.

the skin, with a favorable prognosis under treatment. Contrasted with these cases are others in which, from the first, there is a carcinoma of ducts or parenchyma, a limited involvement of skin, a diffuse invasion of breast, an unfavorable prognosis, and often a rapid course. It is difficult to accept the conclusion that these two maladies are identical in nature, differing merely in grade of malignancy; but histologic studies show that the lesions are very similar."

It is not the object of this report to enter into the controversy concerning Paget's disease of the nipple. We wish to report our experience with the disease and to emphasize the observation of Paget, namely, that most cases of chronic eczema of the nipple are closely associated with a true carcinoma of the breast.

We have reviewed the records of 20 cases of Paget's disease of the nipple. Through the courtesy of the Surgical Department of St. Luke's

Hospital we have been permitted to study 12 cases in their records. These patients were treated over a period of approximately 23 years (January, 1918–May, 1941), and eight were treated at the New York Hospital over a period of about nine years (September, 1932–May, 1941). The diagnosis in each case was based on the presence of an eczema or excoriation of the nipple which, on histologic section, showed epithelial hypertrophy, subepithelial round cell infiltration and Paget's cells.

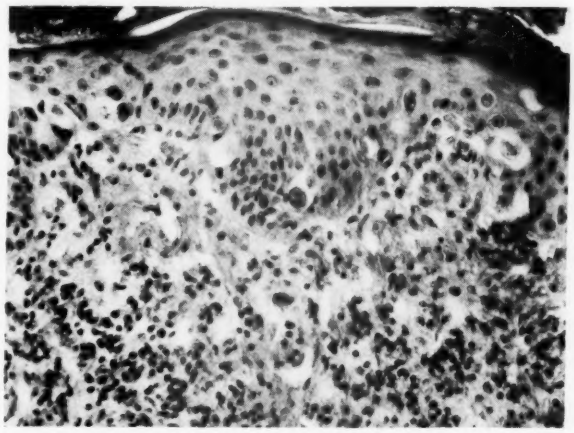

FIG. 5.—Case 2: Section through skin. Shows direct invasion of epidermis by carcinoma cells. Only a few Paget cells in this section. (×280)

As suggested by Ewing, these cases are readily divided into two clinical groups: In the first group (Table I) of 13 cases, all but two of whom were over 50 years of age, the chief complaint of each patient was an eczema of the nipple, usually of long duration. In only three instances was the lesion of the nipple present for less than one year. Section of the breasts, after removal, revealed a definite tumor in eight of the 13 cases, and in three of the eight there were axillary metastases. Of the three patients with axillary metastases, one died six months, and another four years, after operation; the

TABLE I

GROUP I—PAGET'S DISEASE OF THE NIPPLE—CHIEF COMPLAINT: ECZEMA OF NIPPLE

Case No.	Age	Duration of Eczema	Breast Tumor	Mastectomy	Node Involvement	Result
1.	74	6 yrs.	No	Simple	Not removed	Well—2 mos.
2.	59	5 yrs.	Yes	Radical	Yes	Died— 4 yrs.
3.	60	4 yrs.	No	Radical	No	Well—17 yrs.
4.	55	4 yrs.	Yes	Radical	Yes	Died—6 mos.
5.	62	2 yrs.	Yes	Radical	No	Well— 9 yrs.
6.	57	18 mos.	No	Simple	Not removed	Well—15 yrs.
7.	60	15 mos.	Yes	Radical	No	Well— 3 yrs.
8.	50	1 yr.	Yes	Radical	No	Well— 1 mo.
9.	67	1 yr.	No	Radical	No	Well— 2 yrs.
10.	64	1 yr.	Yes	Radical	Yes	Well— 1 yr.
11.	52	8 mos.	Yes	Radical	No	Well—10 yrs.
12.	41	3 mos.	No	Simple	Not removed	Well— 4 yrs.
13.	47	2 mos.	Yes	Radical	No	Well— 3 yrs.

third was subjected to operation only one year ago, and is alive and well, without evidence of recurrence. The remaining ten patients are alive and well, two, for more than 15 years, one, ten years, one, nine years, three for three years, and three operated upon within the past year.

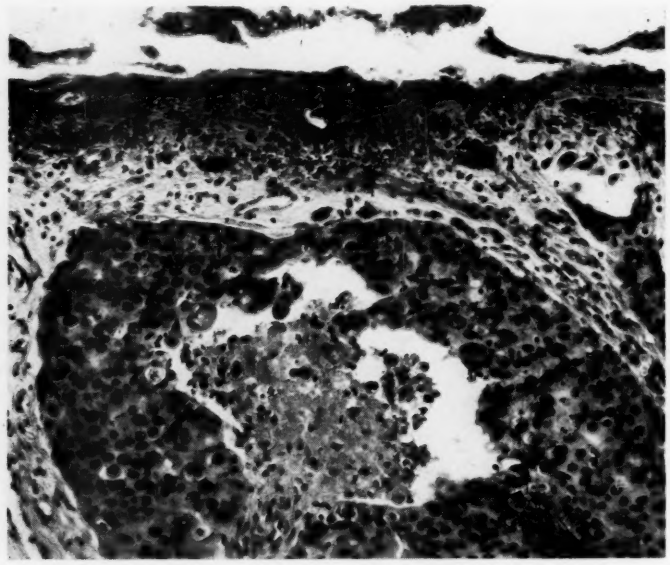

FIG. 6.—Case 2: Section through breast. Shows a duct cell-type carcinoma.

This group of 13 cases emphasizes the close relationship between chronic lesions of the nipple and carcinoma of the breast. It also suggests that carcinoma of nipple origin is slow to metastasize to the axillary lymph nodes and, therefore, forms a favorable group with proper treatment. We agree with Cohn[11] that all lesions of the nipple which do not quickly respond to simple treatment should be subjected to a biopsy which includes a good section of the underlying breast tissue, and if the histologic picture is that of Paget's disease a radical mastectomy should be performed.

In the second group of seven cases (Table II) all the patients were aware of a tumor of the breast at the time they sought medical advice, and only two complained of an associated eczema of the nipple. In fact the nipple lesions were so inconspicuous that in not a single instance was the clinical diagnosis of Paget's disease made. Histologic studies of the nipples, however, revealed changes similar to those of the first group. The second group is also distinct from the first in that the symptoms were of relatively short duration, the average being four months. Four of these patients are known to have died of their carcinomata within three years after operation, one has been alive for one year but has a local recurrence, and the result in the other two is not known.

TABLE II

GROUP II—PAGET'S DISEASE OF THE NIPPLE—CHIEF COMPLAINT: BREAST TUMOR

Case No.	Age	Duration of Tumor	Secondary Nipple Changes	Mastectomy	Node Involvement	Result
1.	46	9 mos.	Yes	Radical	No	Died—3 yrs.
2.	44	6 mos.	Yes	Radical	No	Unknown
3.	50	6 mos.	Yes	Radical	Yes	Died—6 mos.
4.	38	3 mos.	Yes	Radical	Yes	Died—2 yrs.
5.	40	2 mos.	Yes	Radical	Yes	Died—2 yrs.
6.	50	1 mo.	Yes	Radical	Yes	Recurrence—1 yr.
7.	62	1 mo.	Yes	Radical	Yes	Unknown

CONCLUSIONS

From the clinical point of view there appear to be two groups of cases in which nipple changes characteristic of Paget's disease are noted: (1) Those presenting an eczema of long standing, which may or may not be associated with a definite tumor in the breast, and in whom the prognosis is good with early surgical treatment; (2) those who, from the first, apparently have a carcinoma of the breast with secondary invasion of the nipple and in whom the prognosis is poor. Metastasis occurs in both groups, more frequently in the second than in the first.

The close relationship between chronic eczematoid lesions of the nipple and carcinoma of the breast makes it imperative that early and adequate biopsy be made of every chronic nipple lesion. If a diagnosis of Paget's disease is made, regardless of whether or not a definite tumor can be demonstrated in the breast, the patient should be subjected to a radical mastectomy.

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HEMANGIOPERICYTOMA

A VASCULAR TUMOR FEATURING ZIMMERMANN'S PERICYTES

ARTHUR PURDY STOUT, M.D.,
AND
MARGARET R. MURRAY, PH.D.
NEW YORK, N. Y.

FROM THE SURGICAL PATHOLOGY LABORATORY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE DEPARTMENT OF SURGERY, PRESBYTERIAN HOSPITAL, NEW YORK, N. Y.

IN A RECENT COMMUNICATION, the writers demonstrated by the method of tissue culture that the epithelioid cell of the glomus tumor is derived from Zimmermann's pericyte. This is a contractile cell with long processes which wraps itself about capillaries and serves to change the caliber of their lumens. Zimmermann, and others, have suggested that these pericytes are modified smooth muscle cells. The glomus tumor is a complex organoid neoplasm furnished with many axis cylinders, which reproduces in caricature the normal neuromyo-arterial glomus. There occur, however, tumors composed of capillary blood vessels with one or more layers of rounded cells arranged about them, which cannot be called glomus tumors because they lack the organoid features of those encapsulated complex neoplasms, yet differ from simple capillary hemangiomata because of the presence of their perivascular cells. We believe that these cells are pericytes and that these tumors should be distinguished by a specific name and suggest "hemangiopericytoma" as properly descriptive.

In the past, one gathers that such tumors have generally been called hemangio-endotheliomata on the assumption that only the prolific and versatile vascular endothelia could give rise to these rounded perivascular cells. We have never agreed with this opinion but had no alternative suggestion for their origin until we learned about pericytes from the writings of Zimmermann and observed how greatly they differed from endothelia when grown *in vitro*. There are, indeed, vascular neoplasms that may properly be called hemangio-endotheliomata. These are malignant tumors of capillaries featuring the growth of neoplastic endothelia, which in addition to heaping up inside the lumen may invade the wall and proliferate outside but these tumors are very different from hemangiopericytomata in which the endothelia never differ from the appearance of normal endothelial cells.

It is probable also that Schmidt (1937) has included one or possibly two cases of hemangiopericytoma in a group if vascular tumors which, following the suggestion of Orsós (1934), he chooses to call gemmangiomata. Orsós revived the hypothesis of R. Meyer that blood vessels and blood cells are all derived from embryonal pluripotent cells called angioplasts. He then proceeded to describe a number of vascular tumors, some composed in part of capillaries and in part of immature endothelial sprouts without lumens and others

much more complex with both capillaries and immature red and white blood cells. Orsós also included tumors which did not seem primarily vascular at all, and in attempting to follow his lead Schmidt included under the name gemmangioma tumors which seem to us to be xanthoma and liposarcoma. If Orsós had restricted the term gemmangioma to tumors composed of immature capillary sprouts, the term might be acceptable. But since he has chosen to make it cover a heterogeneous variety of tumors which Schmidt has further enlarged, we believe that only confusion will follow any attempt to perpetuate the term.

In our collection of 691 blood vessel tumors, we find nine cases to which the name hemangiopericytoma may be applied in addition to 38 glomus tumors for which the term might also be used. This group of nine tumors is an interesting one because it includes cases showing most of the biologic features exhibited by other vascular tumors including locally persistent aggressive infiltrative growth in one instance and distant metastasis resulting in death in another. In another crucial case, the probable relationship between pericyte and smooth muscle cell is strongly suggested because the cells arranged about the tumor vessels vary all the way from the usual rounded pericyte through an indeterminate phase of spindle shapes to a fully differentiated cell with myofibrils.

The first four cases are all alike histologically, and demonstrate the usual appearance of this neoplasm:

CASE REPORTS

Case 1.—A male, age 45, had a tumor the size of a dressmaker's pin on the dorsal surface of the left ring finger. It looked like a nonpigmented mole. If struck it would bleed and become sore, otherwise it gave no trouble. After an attempt to destroy it by electrocauterization failed, it was excised. Three years later there was no evidence of recurrence. (Case made available by Dr. F. A. Patterson of Norwalk, Conn., and Dr. Gray Twombly, New York.)

Case 2.—When this female infant was born, a small "birthmark" was noted in the skin at the outer margin of the breast. It was excised at the age of six months. The case was not followed. (Case made available by Dr. Howard Meyer, Hackensack Hospital, N. J.)

Case 3.—When this female infant was born, there was a small red spot in the skin of the parietal region. At age three months it had reached a diameter of 1 cm. and was excised. It was quite vascular but did not extend beneath the galea. The case was not followed. (Case made available by Dr. A. O. Severance, San Antonio, Texas.)

Case 4.—Age and sex unknown. Five months before, a blow was received on the shoulder and another one two months later. Following this a lump appeared in the skin and grew larger. It was tender, attached to the skin but otherwise freely movable. It was excised and the case was not followed. (Case made available by Dr. H. Meyer, Hackensack Hospital, N. J.)

Pathologic Characteristics.—All of these tumors are made up of groups of endothelial-lined tubes filled with erythrocytes and of endothelial sprouts without lumens. Both are supported by delicate reticulin fibers outside of which are arranged the rounded pericytes. These sometimes form a single layer or they may be in such numbers that all of the space between neighboring vessels may be filled with them. Some vessels may have no pericytes. No elastic fibers are formed. Like ordinary capillary hemangiomata,

the groups of tumor vessels infiltrate the skin and sometimes the subcutaneous fat to a limited degree (Fig. 1).

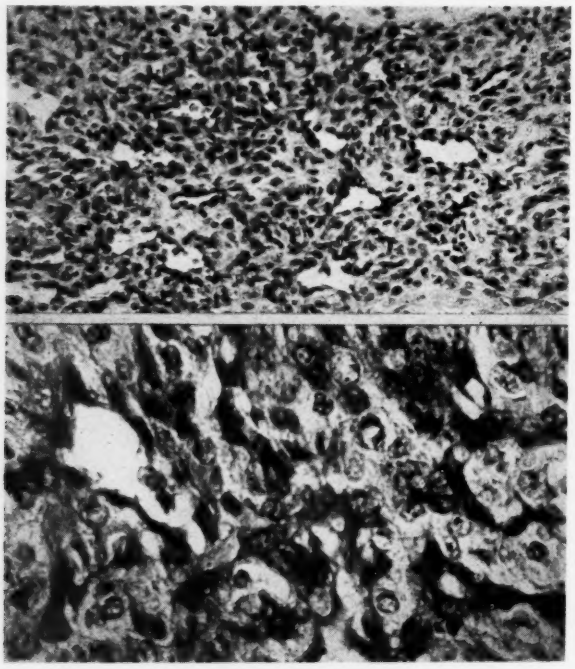

FIG. 1.—Case 1: Above, is shown one of the nodules composed of endothelial-lined capillaries surrounded by masses of pericytes. Below, a detail enlargement from another area showing endothelial sprouts both with and without lumens. The endothelia are deeply stained and are in sharp contrast with the rounded pericytes which are paler and have vacuolated cytoplasms.

The second group includes cases with both rounded and spindle-shaped cells:

Case 5.—At birth, this male infant had a painless nodule, 17x10 Mm., in the right anterior chest wall which did not increase in size. It lay within the pectoralis major muscle and was excised at the age of two months. The case was not followed. The specimen showed a central area of necrosis surrounded by a grayish-white zone of viable tissue, which invaded the muscle to a limited extent. (Case made available by Dr. Beryl Paige, Babies Hospital, N. Y.)

Case 6.—Male. At age 21, his right infra-orbital region was hit with a nail. In a few days a tumor appeared and grew slowly. Three years later it was excised but promptly recurred, and at age 25, it was again incompletely excised. It then grew slowly for 17 years, and more rapidly during the succeeding three years. At age 45, 24 years after onset, it was 4 cm. in diameter. It was soft, not tender and had never been painful. It lay 1 cm. beneath the epidermis, was apparently encapsulated, and extended into the orbit. The cut surface was pale pink, soft, homogeneous, and mottled with hemorrhages. The case was not followed.

Case 7.—Male, age 31. There was a nodule covered with epidermis, pedunculated, and 5 Mm. in diameter, which projected from the auricle and had been present since childhood. There had been recent slight increase in size but no pain. It was excised and the case was not followed.

Pathologic Characteristics.—In Case 5 the tumor is made up of lobules composed chiefly of endothelial-lined tubes often containing erythrocytes. Arranged in close proximity to the endothelia are rounded pericytes in many areas. In some, however, the cells are spindle-shaped and suggest the appearance of smooth muscle but usually lack myofibrils. In several areas, however, it is possible to trace a direct continuity between these elongated cells without myofibrils and characteristic, mature smooth muscle cells with definite myofibrils. Transition forms containing immature myofibrils can be identified (Fig. 2). Case 6 is like Case 5, but no myofibrils can be found and there are no transitions from spindle cells to smooth muscle cells. Case 7 has very few rounded pericytes and is composed largely of spindle-shaped cells which are heaped up in considerable numbers so that the endothelial-lined tubes are often quite widely separated.

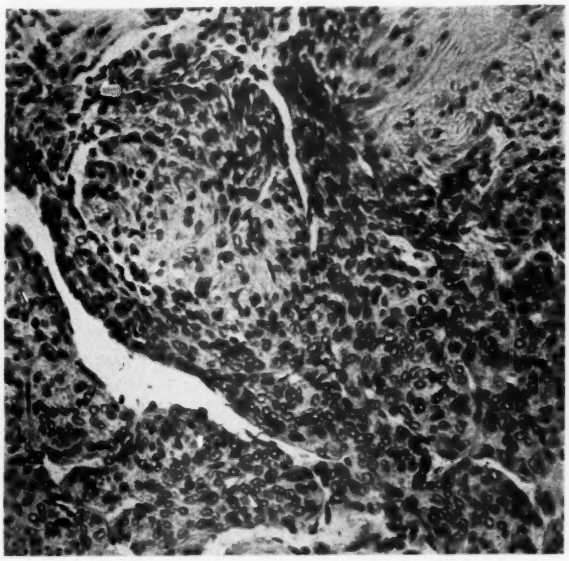

FIG. 2.—Case 5: Numerous endothelial-lined capillaries are surrounded by rounded pericytes. In places, these blend with elongated cells which approximate the appearance of smooth muscle cells.

These three cases seem to us to be of importance because they suggest very strongly that the pericyte is a modified smooth muscle cell. The next step in differentiation would be to have no rounded pericytes but only spindle-shaped cells, some of which were without myofibrils, while the majority were fully differentiated smooth muscle cells. Such tumors exist and have been reported by one of us (A. P. S.) in a paper on cutaneous leiomyomata. They were there called vascular leiomyomata, and the fact that some of the cells contained no smooth muscle fibers was not brought out because its importance was not appreciated. The large amount of smooth muscle formed in the spaces between the vessels was the reason for calling these tumors leiomyomata, but there is no doubt that they are related closely to this present group of hemangiopericytomata.

The next case shows that tumors of this class can exhibit aggressive, infiltrative growth bordering on malignancy:

Case 8.—Male. At age 42, a small tumor appeared on the lateral aspect of the left index finger. This ruptured spontaneously, with a bloody discharge. During the next 11 years he had ten local operations in attempting to remove all of the tumor, but none succeeded. It always reappeared, extending slowly toward the base of the finger and forming multiple nodules. At age 53, the finger was disarticulated at the metacarpophalangeal joint. The tumor reappeared in the stump, and a year later the cicatrix together with the distal three-fourths of the index finger metacarpal bone was resected. This was successful in removing all of the tumor. He was seen 14 years later, without evidence of neoplasm and finally died of an unreported cause at age 70, 28 years after the tumor first appeared, and 16 years after the last operation.

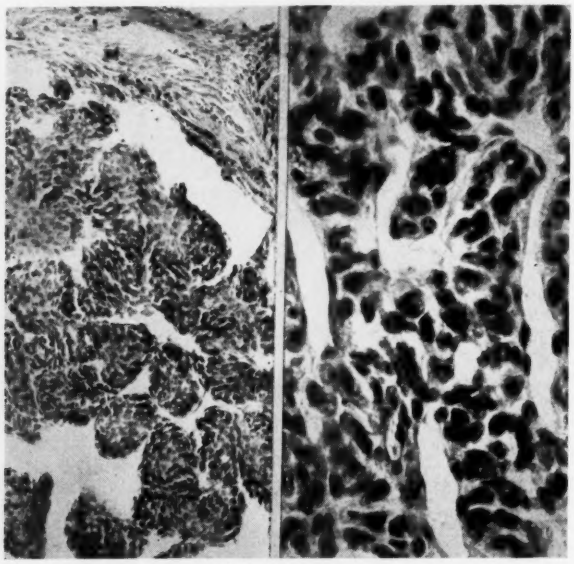

FIG. 3.—Case 8: Appearance of the tumor in the stump of the amputated finger. At the left, a nodule of tumor with its endothelial tubes surrounded by pericytes. At the right, a detail in higher magnification.

In this tumor the pericytes are always the most conspicuous feature of the growth (Fig. 3). Capillaries and endothelial sprouts are present but as the sprouts are not canalized they are inconspicuous and can easily be overlooked. Nevertheless, they are always formed and the tumor grows characteristically in lobules made up of aggregations of vessels and sprouts with their satellite cells. Grossly, the tumor nodules were soft and pallid, presumably because they contained so little blood. Unfortunately, the tissue obtained from this tumor was never properly fixed and our cytologic studies leave much to be desired.

The last case is an example of late metastasis and death in a hemangiopericytoma that exhibited a number of interesting variations in the primary growth:

Case 9.—Colored female. At age 34, she first noted a swelling on the medial aspect of the lower part of the right thigh. This grew considerably during the next three years until, finally, it became slightly painful on walking and its bulk caused slight limitation

of motion at the knee joint. It was excised at age 37. The tumor was irregularly ovoid and measured 14x7x6 cm. It was intimately attached to the periosteum of the anterior aspect of the femur between the condyles and to the mesial aspect of the capsule of the knee joint. Throughout the rest of its extent, it was enclosed by a capsule. The tumor

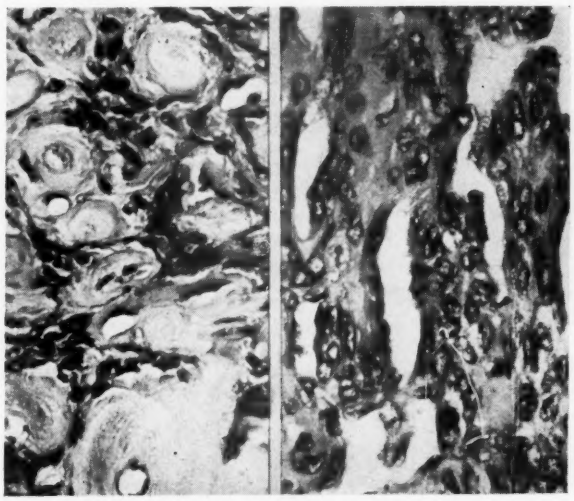

FIG. 4.—Case 9: Detail from the primary tumor. At the right, endothelial tubes and pericytes, without much fibrosis. At the left, the capillaries are surrounded by dense, thick collagen sheaths and the pericytes pushed aside and atrophic.

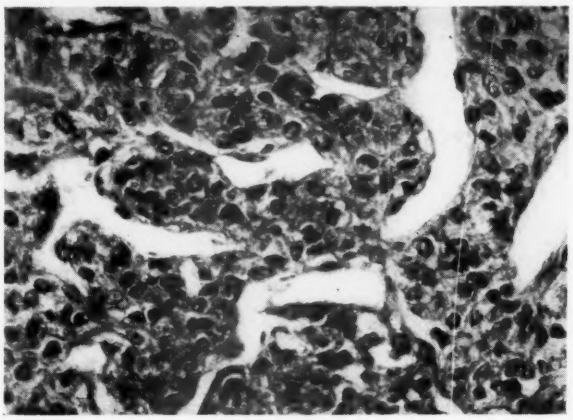

FIG. 5.—Case 9: Metastasis in the liver. The tumor maintains the relationship of capillary tube and surrounding pericytes but the fibrous elements are much less.

was composed of many pale and reddish nodular masses. There was never any local reappearance but four years later there were found five nodules in the right lobe of the liver, varying from 1 to 4 cm. in diameter and one of them was biopsied. The iliac and celiac nodes were enlarged. The liver was treated postoperatively with small doses of roentgenotherapy, with relief of pain. Seventy-four months after the first operation there was roentgenographic evidence of metastases in the third and fifth ribs, and these also received roentgenotherapy. She went progressively downhill, and finally died seven years and four months after the first operation, and three years and four months after proof of liver metastases. No autopsy was done.

Pathologic Characteristics.—Histologically, the primary tumor is composed of capillary tubes and sprouts which in some areas are surrounded by layers of rounded and occasionally elongated cells in the customary fashion. Where recent growth has occurred, the capillaries are simple endothelial tubes supported by reticulin fibers, but where the tumor is older, the endothelia are surrounded by thick compacted collagen sheaths of a hyaline aspect in ordinary stains and the tumor cells are outside of these (Fig. 4). The growth of pericytes, occasionally, is so massive that the vessels are widely separated but, as a rule, the vascular nature of the tumor is never in doubt. No myofibrils are recognized in any of the tumor cells. Laidlaw stains show a rich reticulin framework which surrounds most of the tumor cells.

The vascular aspect of the tumor is clearly shown in the liver metastasis, which is composed of many endothelial tubes surrounded by rounded cells so closely placed that the tumor cells of one unit often touch those of its neighbors (Fig. 5). Most of the tumor cells are surrounded by delicate collagen or reticulin fibers. The aspect of this metastasis closely resembles parts of the original tumor and, histologically, does not appear like a malignant growth.

The hemangiopericytoma thus emerges as a tumor which does not have sufficiently arresting gross features to enable one to recognize it clinically. Except in Cases 2 and 3, in which the tumors involved the skin and resembled other congenital hemangiomata, there is no red color nor are there other gross characteristics suggesting that the growth is one of blood vessels. This is due apparently to the accumulation of pericytes and connective tissue in which the vascular tubes are incased and also to the fact that many of the endothelial sprouts are not canalized and contain no erythrocytes. Otherwise, it behaves very much like other angiomatous tumors in its tendency to begin before birth or early in life, to grow locally sometimes as a circumscribed nodule, sometimes with slow and limited infiltration of surrounding tissues, occasionally with more persistent and aggressive infiltration and rarely with metastasis. Although usually small, it may attain a very considerable size, up to a length of 14 cm. as is shown by Case 9.

The diagnosis can be made by histologic examination. The tumor must be composed of groups of endothelial-lined tubes or impervious endothelial sprouts surrounded by rounded cells with a supporting meshwork of reticulin fibers. The rounded cells may show a tendency to become elongated and in this form poorly defined myofibrils may be found. Usually, the vessels with their pericytes are distinct one from the other, separated by a fibrous stroma, but they may become so closely packed that the pericytes of one vessel may be in continuity with those of its neighbors. One should be very certain, however, that the growth is basically vascular and not a tumor whose cells are nourished by a rich vascular network such as one sees in many tumors of endocrine organs, in some Ewing tumors of bone marrow, and elsewhere.

SUMMARY

A type of vascular tumor has been described, characterized by the formation of endothelial tubes and sprouts with a surrounding sheath of rounded and sometimes elongated cells. The writers believe that these are derived from the capillary pericytes, described by Zimmermann, and suggest that the tumors be called hemangiopericytomata.

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THE PATHOGENESIS OF MIXED TUMORS OF THE SALIVARY GLAND TYPE

LOUIS H. HEMPLEMANN, JR., M.D.,

AND

NATHAN A. WOMACK, M.D.

ST. LOUIS, MO.

FROM THE DEPARTMENT OF SURGERY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, THE BARNES HOSPITAL, AND THE BARNARD FREE SKIN AND CANCER HOSPITAL, ST. LOUIS, MO.

THE CONTROVERSY concerning the fundamental structure of mixed tumors of the salivary gland type has never been settled satisfactorily. Since 1853, when the tumors were recognized as a clinical entity by Paget,[1] the ensuing years have added much discussion as to their nature. In 1859, Theodor Billroth[2] wrote his classic thesis on salivary gland tumors and surprisingly little of morphologic interest has been added since his excellent description. His interpretation of the tumors as mesenchymal growths (accepted with certain modifications by Virchow) held sway for many years, overshadowing the earlier work of Robin,[3] and others, who suggested that the tumors were epithelial. Toward the latter part of the nineteenth century, Billroth's concept of the tumors was challenged, and since then numerous other theories of histogenesis have been presented. One of the best and most inclusive summaries of these theories is that of Hoepfel,[4] to which the reader is referred. Hoepfel divides the theories of the nature of mixed tumors into three main groups, based on the interpretation of the parenchymal elements of the tumors:

(1) In this class fall all of those conceptions holding that the parenchyma is mesenchymal in origin. Billroth originated this idea. Virchow[5] felt that the epithelium was derived from mesenchyme, due to the ability of the connective tissue elements to undergo metaplasia into epithelial tissues. Others believed that the tumors were composed of endothelial cells, and for many years the tumors were called "endotheliomas."

(2) In this large group fall those theories considering the parenchyma as derived from epithelium. However, while there is agreement concerning the origin of the parenchyma, there are differences in interpretation of the nature of the stroma. These latter opinions may be divided into five subgroups, which regard the stroma in the following ways: (a) The stroma takes origin by displacement of mesodermal germ tissue at the same time in embryonic life as do the ectodermal elements. (b) The stroma is mesodermal tissue which is formed as the result of the improper local "organizer" action of the epithelium on undifferentiated mesoderm. This utilizes the present-day knowledge of experimental embryology. (c) The stroma is a mesodermal tissue which has been formed by metaplasia of the epithelial parenchyma. (d) The stroma is epithelium which has been modified as a result of its secretory products so that it resembles cartilage and other mesodermal tissues. (e) The stroma is a

"hybrid" substance arising through the union of epithelial and mesothelial tissues with their secretory products.

(3) In this small group are included those persistent ideas that the parenchyma possesses epithelial as well as endothelial components. Evidence in support of such a conception has been so vague that little acceptance is given this idea at the present time.

In the American and English literature perhaps the most generally accepted theory held at present is that mixed tumors are true epithelial tumors without mesodermal elements. There are several standard textbooks of pathology that subscribe to this conception. However, during the past decade there has been a trend, particularly in the German literature, to regard the tumors as primary epithelial growths which have induced abnormal differentiation of the undifferentiated mesoderm.

When one examines the evidence for all of these theories mentioned above, it is apparent that they are based on individual interpretations of the morphology of the pleomorphic tumors. One needs only to examine sections of mixed tumors to realize how unsatisfactory and difficult morphologic study may be. All variations within a tissue and gradations between tissues are found. To illustrate the difficulties involved in histologic study of the tumors, let us consider their microscopic appearance very briefly.

HISTOLOGIC FEATURES OF THE MIXED TUMORS

The parenchyma of the tumors is unquestionably epithelial and appears in many variations. The small oval or spindle cells growing in sheet formation represent one of the most common types. They closely resemble the type of cell seen in basal cell carcinomata. Occasionally the cells are larger, with vesicular nuclei. They often form acini, which may contain mucus. Some of the individual cells show evidence of secretion in the form of intracellular droplets of mucus. Epithelial cells with intercellular spinous processes in bulbous formation with typical epithelial pearls are often found. Some of the epithelial cells form pseudorosettes, resembling embryonic ducts more closely than they do adult epithelial structures. Occasionally nests of epithelium show a peculiar type of degeneration of their central portions with the resultant formation of star-shaped cells similar to those seen in ameloblastomata. These cells may be widely separated but usually remain connected by long intercellular processes.

The epithelial cells are separated by a stroma, the appearance of which suggests mesodermal origin. The most characteristic form of the stroma is the chondromyxomatous tissue. The myxomatous tissue bears a striking resemblance to the connective tissue found in the umbilical cord, and that occasionally seen in chondrosarcomata. It is composed of branching cells embedded in a matrix of homogeneous mucoid substance. The cell bodies are usually triangular in shape with long, branching pseudopodia. The amount of cytoplasm enclosing the deeply-staining nuclei is small but the branching processes, of which there are usually two or three, extend far out into the

intercellular substance. Often there are additional more delicate fibrillary processes arising from other parts of the cell bodies. These cells may be widely separated or may form strands of two or three. The cartilaginous or "pseudocartilaginous" tissue differs from adult cartilage only in the absence of the characteristic pattern. Other tissues found in the stroma resemble hyalinized connective tissue, with eosinophilic, dense homogeneous matrix containing a few elongated cell bodies. Adult fat cells and small islands of bone are occasionally found deep within the tumor nodules.

The types of tissue mentioned above are well recognized. Their relationship, however, is interesting and peculiar to this type of tumor. Epithelial tissue of one type appears to change gradually into another type. Myxomatous tissue merges into cartilaginous tissue or into hyalinized connective tissue. Even more puzzling than this, however, is the anatomic relationship between the epithelium and the stroma. Where the epithelium is well differentiated there is a sharp line of demarcation, but in many places there is gradual, apparent transformation of frank epithelium into myxomatous tissue. In these transitional zones the cells cannot be said to be either epithelial or myxomatous.

It is this unusual relationship of tissues which appear to be derived from separate germ layers that is responsible for the confusion regarding the histogenesis and nature of these tumors. It seems incredible that epithelial cells can resemble mesenchymal tissues so closely. Yet if there are two types of tissue how can one explain their intimate relationship and apparent transitions from one into another? A morphologic study of the tissues has failed to provide a satisfactory answer to this question.

HISTOCHEMICAL INVESTIGATION OF TISSUE MUCOIDS OF MIXED TUMORS

In considering a group of mixed tumors of the salivary gland type, the futility of further study of their morphology at once became evident. It occurred to us that a chemical investigation of the mucoid material in the parenchyma and stroma might be of value in determining the nature of the tissues and, accordingly, a microchemical study of epithelial and mesodermal mucoids was undertaken by one of us (L. H. H.[6]). Before describing the results of this study it will be of value to discuss briefly the chemistry of the mucopolysaccharides. For a more detailed discussion the reader is referred to the classic monograph of Levene,[7] as well as the more recent articles of Meyer.[8]

Mucoproteins are complex proteins composed of two radicals, one a protein molecule, the other a carbohydrate complex. It is the latter group which is responsible for the specificity of the molecule and hence its chemical and staining properties. According to Levene, the prosthetic groups are composed of a hexosamine fraction conjugated with sulfuric, glucuronic and acetic acids. They exist as several modifications of one general type, the best known ones being chondroitin sulfuric acid and mucoitin sulfuric acid. These compounds are similar in structure and composition, differing only in the carbohydrate

fractions (which are probably isomeric hexoses) as well as in the attachment of certain side-chains.

Despite the chemical similarity of these mucoproteins, their distribution in nature is widely different. Chondroitin sulfuric acid has been isolated only from mesenchymal tissues such as cartilage, bone, tendon, sclerae, umbilical cord, and the wall of the aorta. The chondroitin sulfuric acid protein complex, therefore, has been said to be the mucoprotein of connective tissue,[8] and is probably responsible for the staining characteristic of the mesenchymal mucoids. Mucoitin sulfuric acid on the other hand has been found in the mucin of salivary glands and gastric mucosa, in serum mucoids, ovomucoid, Wharton's jelly, vitreous humor, and in the cornea. Recently, however, evidence has been presented that the mucoids of Wharton's jelly, and egg white do not contain mucoitin sulfuric acid. The subject of mucopolysaccharides has been further complicated by the identification of sulfate-free mucopolysaccharides in Wharton's jelly and salivary gland mucin.[9] It might be said, however, that the mucoitin sulfuric acid complex is a product of epithelial secretion, while chondroitin sulfuric acid protein is limited to those connective tissues of mesenchymal origin.

Because of the chemical similarity of their prosthetic groups, the tissue mucoids stain alike with basic and metachromatic dyes. For this reason it has not been possible to distinguish between them by ordinary staining procedures. Recently, one of us (L. H. H.[6]) has devised certain microchemical methods by which mesenchymal and epithelial mucoids (presumably chondroitin sulfuric acid and mucoitin sulfuric acid complexes, though the simpler mucopolysaccharides known to exist in epithelial mucus, may play some rôle in the chemical reaction) can be differentiated in fixed tissue sections. One of these is a titration method utilizing the difference in affinity of the protein complexes for very dilute aqueous solutions of the metachromatic dyes. Serial sections of formalin-fixed tissue are stained with increasing dilutions of toluidine blue or polychrome methylene blue. There is a definite range of dilutions (in the case of polychrome methylene blue about 1:200 to 1:1400 depending on the temperature, the age, and the method of preparation of the stock solutions) in which the chondroitin sulfuric acid complexes stain with almost maximum intensity while the epithelial mucoids fail to stain. In the control experiments it has been possible to stain cartilage, chondrosarcomatous tissue and the mucoid degenerative products in the walls of arteries with dyes of the proper dilution while the epithelial glands and secretions of the respiratory, gastro-intestinal and biliary tracts and salivary glands failed to stain unless stronger solutions were used. This is a delicate method and requires considerable experimentation with control tissues to obtain the proper dilution for good differentiation.

Another method of differentiating the mucoids is based on the greater resistance of the mesenchymal mucoids to hot acid. Incubating paraffin cut-sections of tissue with dilute solutions of sulfuric acid changes the tissue mucoids in such a way that they no longer stain with the metachromatic dyes.

This, presumably, is due to the breakdown of the acid complex, as the characteristic color is said to be dependent upon the sulfuric acid ester linkage. The rate of breakdown is different for the mesenchymal and epithelial mucoids. Care must be taken that large enough quantities of acid be used to rule out differences due to disproportionate concentration of mucoid substance.

FIG. 1.

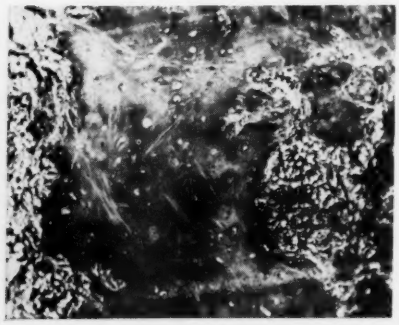
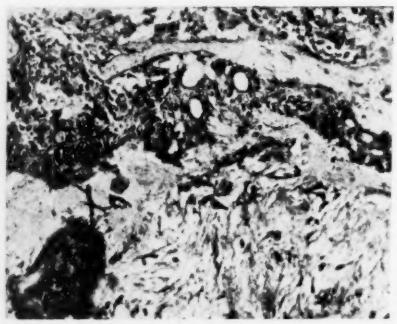


FIG. 2.



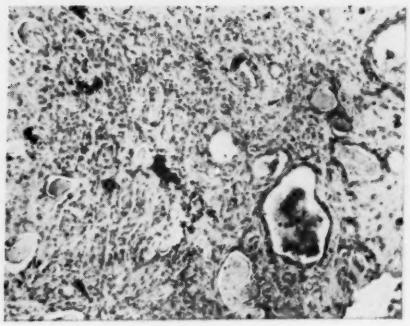


FIG. 3.

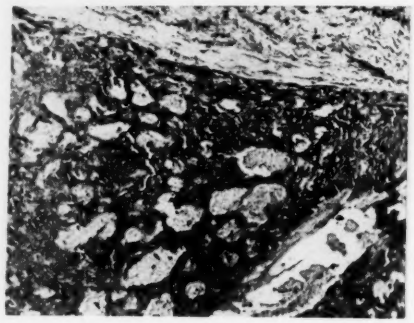


FIG. 4.

FIG. 1.—Mixed tumor of the parotid gland stained with polychrome methylene blue 1:340. The matrix of the cartilaginous tissue stains bright reddish-purple (photomicrograph was taken with a green filter to emphasize this color), while the remaining tissue stains blue or green. Epithelial mucus, as represented by gastro-intestinal biliary tract and salivary glands, failed to stain with this dilution.

FIG. 2.—Mixed tumor of the parotid stained with differential polychrome methylene blue solution described in Figure 1. The wavy strands in the upper right portion of the photomicrograph represent reddish-purple mucus of a myxomatous area. Intra-acinar mucus failed to stain with this dilution.

FIG. 3.—Mixed tumor of salivary gland stained with 1:260 aqueous dilution of polychrome methylene blue. Note the intra-acinar mucus which failed to stain with the differential solution used in Figures 1 and 2. The intracellular mucus in goblet cells of adjacent salivary gland behaved as the above type of mucus.

FIG. 4.—Mixed tumor of the parotid gland stained with 1:260 polychrome methylene blue. The mucus within the acini also failed to stain with the differential solution used in Figures 1 and 2. This type of mucus as well as that in Figure 3 was destroyed by hot sulfuric acid in the same manner as the initial types of epithelial mucus.

While the end-points of this method are not as sharp as they are in the first, the results are consistent, and can be used in the evaluation of the chemical nature of the mucoids.

Both methods show that the mucoid in the myxomatous and cartilaginous areas in mixed tumors of the salivary glands behaves exactly as does the chondroitin sulfuric acid complex in skeletal cartilage, chondromata, chondrosarcomata, and in the walls of arteries showing mucoid degeneration (Figs.

1 and 2). The mucoid within the acini stains exactly as does the mucoprotein complex in the mucin of the salivary gland, gastro-intestinal and respiratory tracts, as well as that in mucoid carcinomata of the intestine (Figs. 3 and 4).

From the results of these experiments, it seems justifiable to conclude that the mucoid substance in the myxomatous and cartilaginous areas is a chondroitin sulfuric acid complex while that secreted by the epithelial cells of the tumors is a different mucoprotein, probably mucoitin sulfuric acid complex as well as perhaps simpler mucopolysaccharides.

Since the mucoid in the cartilaginous and myxomatous areas is a mesodermal mucoprotein, presumably chondroitin sulfuric acid, and since the tissue presents the morphologic appearance of mesodermal structures, it is probable that these tissues are truly mesodermal. It does not seem likely, as Techouyeres[10] suggests, that there is a reciprocal mutation between the chemical forms of mucoitin and chondroitin sulfuric acid. This chemical change, involving a special rearrangement of a molecule and perhaps other changes, has never been shown to occur. Similarly, the metaplasia of epithelial cells into true cartilage and myxomatous tissue after histodifferentiation has taken place is contrary to present embryologic concepts. We conclude, therefore, that there are two types of tissue, mesenchymal and epithelial, in mixed tumors of the salivary gland type.

It is not possible to say whether the myxomatous areas represent phases of rapidly growing tissues or whether they are areas of degeneration or the result of local vascular change. They are usually quite avascular, though one occasionally sees blood vessels within such an area. The similarity between such myxomatous tissues and certain types of chondrosarcoma is striking. The similarity is more than just a structural one. When stained with dilute acid solutions of ortho-Capri blue (an oxidation production of methylene blue*) the branching type of cell structure is demonstrated unusually well. The intercellular substance of myxomatous and chondrosarcomatous tissue fails to stain with the Capri blue, whereas that in adult cartilage stains intensely. With transformation from myxomatous to adult tissue there is a gradual appearance of the stainable substance (Figs. 5 and 6). The chemistry of the intercellular matrix of cartilage has not been worked out well enough to enable us to understand this completely, but it is quite possible that this stainable substance is chondro-albuminoid. Very little is known of this substance except that it is an albuminoid closely related to osseo-albuminoid, and similar in many respects to elastin and keratin. The ground substance of cartilage, the keratin layer of epithelium, the elastic layer of blood vessels, cell nuclei and cytoplasm, hyalin and collagen fibers, serum and egg albumin, epithelial mucoid and serous secretions are all stained intensely by Capri blue. The intercellular substance of the myxomatous areas in the mixed tumors, which stains intensely with mucoid stains and that in the histolog-

* The dye was prepared by boiling an aqueous solution containing several drops of 1:100 o-Capri blue and several drops of dilute hydrochloric acid per 50–60 cc. of water.

ically similar chondrosarcoma, are the only protein substances which have been found not to take the blue stain.

FIG. 5 A. FIG. 5 B.

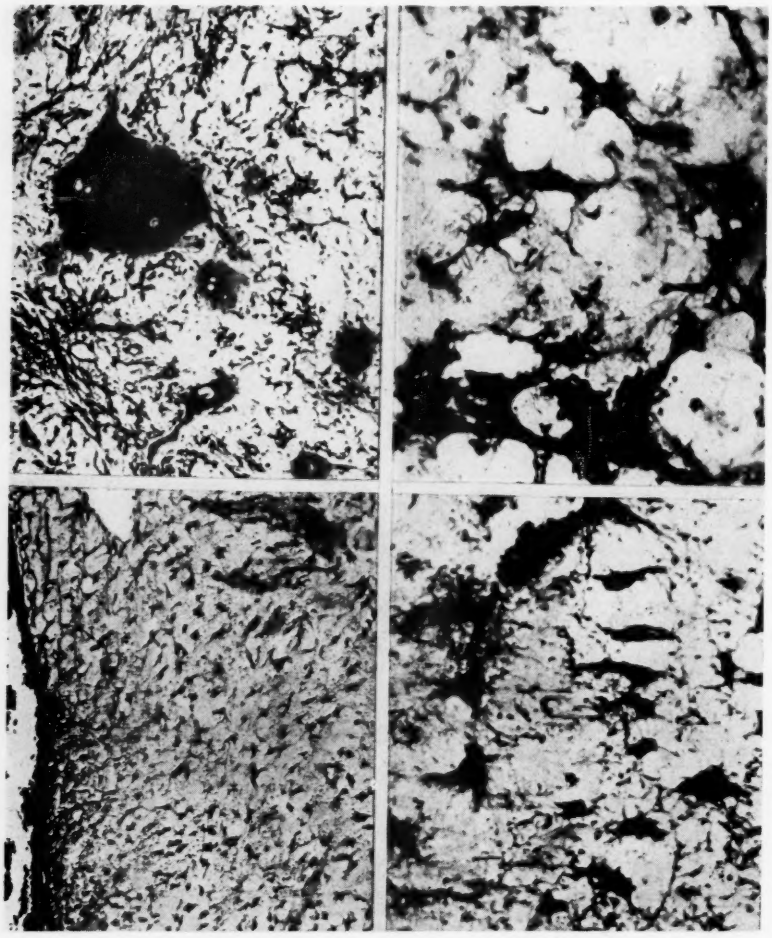


FIG. 6 A. FIG. 6 B.

FIG. 5.—(A) Mixed tumor of the submaxillary gland stained with ortho-Capri blue. Note that the intercellular substance of the myxomatous tissue fails to stain while that of the small island of cartilage is deeply colored.

FIG. 5.—(B) Higher magnification of myxomatous cells showing details of branching structure.

FIG. 6.—(A) Chondrosarcoma of the chest wall stained with ortho-Capri blue. Note that the intercellular substance fails to stain as is the case in the myxomatous tissue of Figure 5. A. Note also the similarity of structure between these cells and those in the myxomatous areas of the mixed tumor.

FIG. 6.—(B) Higher magnification showing similarity to Figure 5 B.

PATHOGENESIS OF THE MIXED TUMORS

If it is accepted that there are two types of tissue in mixed tumors, certain theoretic concepts as to their pathogenesis can be formulated. In view of the presence of two different types of tissue, both of which lack normal differentiation, a failure of normal development seems probable. Evidence continues to

accumulate in support of the fact that normal development depends upon a closely integrated interrelationship between all tissues involved. Functional inadequacy on the part of one tissue at any phase during development may result in structural changes in all tissues concerned subsequently. Such "organizer" or "provocative" action of epithelium on the undifferentiated mesoderm, and *vice versa*, in the formation of certain types of tumors has been suggested before. This view has been proposed by Norrenbrock,[11] after Schürmann and Pflüger's work on the histogenesis of craniopharyngiomata. Such an explanation has been used for mixed tumors of other regions of the body. Schmidt[12] has applied this principle to mixed tumors of the breast, and Möller,[13] and, more recently, Womack and Graham,[14] have used it to explain certain tumors of the lung.

In line with embryologic evidence, the buccal ectoderm of the salivary gland *anlage* probably affects the surrounding buccal mesoderm. In turn, differentiation and development of the ectoderm is probably influenced by the buccal mesoderm. There is considerable evidence that even adult epithelium retains a certain amount of "organizer" influence. Huggins[15] has shown that bladder epithelium is capable of causing differentiation of adult fibrous tissue into bone. This indicates that there are undifferentiated cells in adult fibrous tissue capable of formation of more highly specialized structures. That fibrous tissue is capable of influencing the growth and differentiation of epithelium is shown by the experiments of Drew.[16] He has found that tissue cultures of kidney epithelium and cancer cells from breast carcinomata grow in sheet formation unless fibrous tissue cells are present in the culture. In the latter case, the tumor cells differentiate to form duct-like structures. There is nothing specific in the buccal mucosa which possesses the properties of influencing the differentiation of mesoderm in the manner seen in mixed tumors of the salivary gland type, since the epithelium of the lacrimal gland and skin are capable of similar tumor formation.

The experimental disturbance of tissue environment of the embryo has been shown to lead to structural malformations.[17] It is possible that some such disturbances may lead to development of mixed tumors of this type. The time during embryonic life that such a disturbance occurs, as suggested by Li and Yang,[18] would account for the degree of differentiation which the tissues show. Those occurring earlier in life have the greater potentialities of differentiation.

This interrelationship of tissues has been almost completely ignored in the case of mixed tumors of the salivary gland type, but has been used to explain the development of teratomata.[19, 20] This utilization of the "organizer" conception regards the tumors as a result of primary epithelial maldevelopment, with mesodermal differentiation secondary to this epithelial disturbance. Though the application of this theory to mixed tumors of the salivary glands is not subject to experimental proof at present, it seems to us to be the most rational and is thoroughly in keeping with present-day embryologic tenets.

CONCLUSIONS

(1) The theories of the pathogenesis of mixed tumors of the parotid gland are briefly summarized.

(2) A method is described by which, with special staining technics, mesenchymal mucus can be differentiated from epithelial mucus. Both of these substances are found to be present in mixed tumors of the parotid gland.

(3) In view of the fact that epithelial and mesenchymal mucoids are believed to be identified, it is suggested that two tissue components are represented in these tumors, and that the tumors are, therefore, truly mixed tumors.

(4) It is suggested that the origin of these tumors might be best explained on the basis of embryonic alteration in tissue relationships, in accordance with the "organizer" theory of Speeman.

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ADENOLYMPHOMA OF THE PAROTID GLAND

JULES ALAN PLAUT, M.D.*

NEW HAVEN, CONN.

FROM THE DEPARTMENT OF SURGERY, YALE SCHOOL OF MEDICINE, AND THE TUMOR CLINIC, NEW HAVEN HOSPITAL, CONN.

ADENOLYMPHOMA is one of the rarer salivary gland tumors. Although several times reported in the pathology literature, it is less well known to clinicians. The purpose of this paper is to discuss the neoplasm from the standpoint of the latter group.

In the last 50 years there have been some 48 cases of the tumor described. In addition to these, however, there are many which have been diagnosed but not reported. Carmichael, Davie, and Stewart[2] mention several in addition to their own eight examples, and others have been studied by Klemperer,[7] Stout,[13] and Weller.[15] The figures to be quoted in this communication are gathered from all the reported instances, plus 16 additional previously unpublished cases. With the increasing interest in Tumor Clinics, other cases will undoubtedly turn up, and occasion the consideration of appropriate therapy. More data are needed concerning the life history of this tumor, the relative proportion of benign to malignant cases, the incidence of recurrences, the effectiveness of surgical excision, the need (if any) for supplementary radiation, and the choice between surgery, radiation, and other therapeutic procedures.

Age Incidence.—The great majority of patients were middle-aged or over. Eighty-four per cent of the patients were age 40, or more, with 75 per cent in the fifth, sixth, and seventh decades. At the extreme ends were a child of two and one-half years and a man age 92. The average age was 52 years (Table I).

TABLE I

AGE INCIDENCE

Years	No. of Cases
1– 10	2
11– 20	2
21– 30	1
31– 40	5
41– 50	13
51– 60	20
61– 70	13
71– 80	4
81– 90	0
91–100	1

Youngest—2½ years.
Oldest—92 years.
Average—52 years.

Sex.—Of the 62 cases where the sex was stated, 50 were males and 12 females. The male to female ratio is, therefore, almost five to one.

Duration of Symptoms.—Adenolymphomata are slow growing tumors.

* National Cancer Council Fellow.

The duration of symptoms varies widely, ranging from a few months to 30 years. Table II shows that about 80 per cent of the patients complained of a mass which had been present for from several months to four years.

TABLE II

DURATION OF SYMPTOMS

(where definitely stated)

	No. of Cases
1– 6 months	8
6–12 months	13
1– 2 years	6
2– 3 years	6
3– 4 years	4
4– 5 years	1
5–10 years	3
10–15 years	1
More than 15 years	2

Clinical Course.—In general, it may be said that the tumors are present for at least several months before a physician is consulted. During this time the swelling may vary somewhat in size, but does not change very much. At some time, however, the growth-rate has usually accelerated, probably due to rapid accumulation of fluid in the cystic spaces, and it is then that the patient has become concerned and sought professional advice.

The diameter of the tumor at the time of the first examination varies from one to four or five centimeters, and is usually decribed as being the size of an almond, a cherry, or even a small orange.

In consistency, the tumors are usually firm and solid. Rarely they are hard; sometimes grossly cystic and fluctuant. The growths are ordinarily attached to the deeper structures, but not adherent to the skin. Consequently, the latter can be moved over the underlying tumor, but the mass itself cannot be shifted.

Except when secondarily infected, there is no tenderness on palpation, nor are the tumors usually painful. Occasionally, when the mass is undergoing a comparatively rapid growth, there may be some local discomfort. This, however, is inconsiderable, and confined to the tumor site.

Usually the mass has been described as over the angle of the jaw, in the region of the parotid gland. Occasionally, it lies along the ramus of the mandible, and in a few instances is retro-auricular. One case, an exception, is described as being in the neighborhood of a submaxillary gland.[16] Another, reported by Freshman and Kurland,[3] was in the neck, along "the anterior edge of the superior portion of the left sternocleidomastoid muscle."

The number of cases is about evenly divided between the left and right parotid regions.

With two exceptions the tumors have all been unilateral. The first instance of bilateral involvement was reported by F. L. Niño,[10] in 1940. This author has recently reported six cases of adenolymphomata seen in the last 11 years. This represents 10 per cent of the total number of parotid tumors observed at the Clinico-Surgical Institute of the University of Buenos Aires.

The first of the author's cases is bilateral. The second known instance of bilateral involvement occurred in a patient of Dr. A. W. Oughterson's, at the New Haven Hospital, treated in July, 1941, and previously unreported.

Histology.—Though it is not within the scope of this report to deal at length with the pathology of adenolymphoma, a brief word may be said about the gross and microscopic appearance of the tumor.

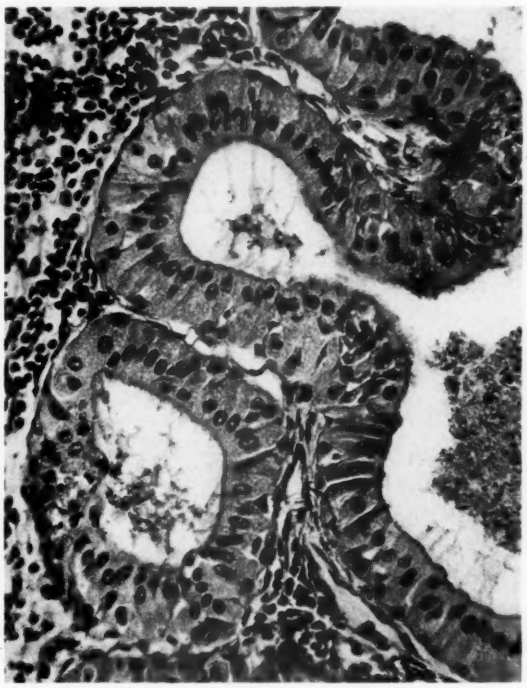

FIG. 1.—Adenolymphoma: Cyst wall. (High power)

The neoplasms vary in shape but are usually spherical or ovoid. They have a lobulated, smooth surface, which is usually covered by a thin, adherent capsule. In almost all instances this completely surrounds the mass and separates it from the parotid. Exceptionally, the capsule is incomplete, and then the tumor infiltrates the parenchyma of the gland. The substance cuts with ease, revealing a gray-pink cut surface, which is often finely granular and pitted with tiny cystic spaces. The latter vary in diameter from the size of a pinhead to several millimeters or more. From some of the cysts a serous fluid may be expressed.

Microscopically, the stroma is made up of lymphoid tissue with large germinal centers. In the midst of this are numerous and various-sized cysts. Many of these contain papillary projections. The cysts are lined with a double layer of epithelium (Fig. 1). The inner of these layers is usually made up of tall, cylindrical cells. These have a finely granular cystoplasm which

stains pale pink with hematoxylin and eosin. The nuclei are apical, basophilic, and vesicular. Warthin[14] described cilia, but they have not been found by others. Between the bases of the tall cells, and less numerous, are small cuboidal cells. These, too, have a pale, granular, acidophilic cystoplasm. Their nuclei are centrally located and vesicular. Many of the cysts contain an amorphous pink material and cellular débris. Others are devoid of secretion. There are few or no mitotic figures. All-in-all, the appearance is that of a benign neoplasm. There are, however, two cases which are reported as showing definitely malignant areas.[11, 12]

As pointed out by Carmichael, Davie, and Stewart,[2] there are variations in the microscopic appearance of the tumor. This is in agreement with Klemperer's[7] view that the term adenolymphoma suggests a group of closely related neoplasms rather than a fixed histologic pattern. The three cases reported herewith fit in with the group of variations, yet quite definitely belong to the category of adenolymphomata.

Therapeutic Procedures.—

(1) *Excision Alone:* Of the 40 case reports which included the nature of the therapy employed, 38 consisted of excision alone. In two cases where the tumors were completely removed by excision, keloids developed in the scars. These were treated with a radon bulb or roentgenotherapy after the excision.

(2) *Excision, Followed by a Recurrence and Then Secondary Excision:* There was one instance of this. The patient, under the care of Dr. C. V. Young, of Bradford, England, had a recurrence of the original tumor three years after local excision. The recurrent tumor was excised ten years after the original operation. According to a communication from Dr. M. J. Stewart, of Leeds, the histology of the original and recurrent tumors was the same, except for some areas of squamous metaplasia in the recurrent tumor.

(3) *Excision Followed by Roentgenotherapy:* There was one patient so treated. He was a male, age 64, who had an adenolymphoma partially excised in the Philippine Islands, May 23, 1939. One week later, because all the tumor had not been removed, he was given ten roentgen ray exposures, totaling 1,250 r. During the subsequent month, the tumor continued to enlarge. He was given two more roentgen ray treatments, and then referred to the Memorial Hospital, New York. The diagnosis was confirmed from a submitted slide. No further therapy was administered because the patient developed rectal bleeding, and he returned to the Philippine Islands. A letter received from his physician, one year later, stated that the "remaining tumor is hardly palpable."

(4) *Irradiation Alone:* No cases were treated this way.

Complications.—There has been only one reported case of a recurrent tumor. As mentioned above, this was removed by a secondary excision. Histologically, only two instances of definite malignant changes have been reported. This comprises about 3.3 per cent of all known examples of adenolymphoma, the vast majority of which are undoubtedly benign.

One additional case deserves mention. A male, age 54 (Memorial Hospital, Case No. 57792—1939), had an excision of a papillary adenolymphoma in the region of the right parotid gland in 1939. Two weeks before operation a node had been felt beneath the right sternocleidomastoid muscle. About one week following the excision, he developed many enlarged nodes in the right side of his neck. One of these was biopsied and diagnosed as reticulum cell lymphosarcoma. He then developed palpable bilateral axillary nodes. Thereupon, he received deep roentgenotherapy (250 K.V.) to both sides of the neck and both axillae. In April, 1941 (one year and eight months after the original excision), he had had no recurrence of the parotid tumor, but still had axillary nodes, and was being followed for the reticulum cell lymphosarcoma.

Follow-Up.—Due to the difficulties in communication incident to the present war, information is available on the postoperative course of only 26 patients. Of these, two are too recent to be of significance. The remaining 24 may be analyzed as follows:

TABLE III

ANALYSIS OF 26 CASES SHOWING THE TIME-INTERVAL, WITHOUT RECURRENCE

Time-Interval	No. of Cases
3 months or less	2
3 to 6 months	2
6 months to 1 year	4
1 to 1½ years	2
1½ to 2 years	3
2 to 3 years	2
3 to 4 years	2
4 to 5 years	2
5 to 6 years	2
6 to 7 years	1
9 to 10 years	1
More than 10 years	1
Total	24

TABLE IV

ANALYSIS OF 64 CASES OF ADENOLYMPHOMA OF THE PAROTID GLAND

48 CASES PREVIOUSLY REPORTED

No.	Source	Patient	Age	Sex	Duration of Symptoms	Treatment	Follow-Up
1.	Jaffé, R. H.: Am. Jour. Cancer, **16,** 1415, 1932.		73	M.	3 yrs.	Excision	
2.	Freshman and Kurland: Am. Jour. Clin. Path., **8,** 422, 1938.		63	M.	1 yr.	Excision	Well. No recurrence after 3 yrs.
3.	Warthin, A. S.: Jour. Cancer Res., **13,** 116, 1929.	J. McD. 1931-L-AD	45	M.	"Many yrs.; slowly growing"	Excision	"No information available"

TABLE IV—(*Continued*)

No.	Source	Patient	Age	Sex	Duration of Symptoms	Treatment	Follow-Up
4.	Warthin, A. S.: Jour. Cancer Res., **13,** 116, 1929.	C. 4887-L-AF	60	M.	20–30 yrs.; recent increase in size	Excision	"No information available"
5.	Stout and Kraissl: Arch. Surg., **26,** 485, 1933.	R. M.	61	M.	2 yrs.	Excision	No recurrence after 1 yr.
6.	Stout and Kraissl: Arch. Surg., **26,** 485, 1933.	D. L.	74	F.	4 yrs.	Excision	No recurrence after 3 yrs., 2 mos.
7.	Hildebrant: Arch. f. klin. Chir., **49,** 167, 1898.		41	M.			Not available
8.	Sultan: Deutsch. Ztschr. f. Chir., **48,** 143, 1898.		44	M.			Not available
9.	Morestin: Bull. Soc. anat. de Paris, **4,** 709, 1902.		23	F.			Not available
10.	Lecène: Rev. de chir., **37,** 1, 1908.		40	F.			Not available
11.	Lecène: Rev. de chir., **37,** 1, 1908.		50	M.			Not available
12.	Albrecht and Artz: Frankfurt. Ztschr. f. Path., **4,** 47, 1910.		64	M.		Excision	Author died 1923. Records not available
13.	Albrecht and Artz: Frankfurt. Ztschr. f. Path., **4,** 47, 1910.		12	F.		Excision	Author died 1923. Records not available
14.	Glass: Frankfurt. Ztschr. f. Path., **9,** 335, 1912.		65	M.	1 yr.		Not available
15.	Delangade, Peyron, and Rouslacroix: Bull. de l'Assn. franc. p. l'étude du Cancer, **7,** 370, 1914.		33	F.			Not available
16.	Menetrier, Peyron, and Surmont: Bull. de l'Assn. franc. p. l'étude du Cancer, **12,** 205, 1923.		50	M.	10 yrs.		Not available.
17.	Mazza and Cassinelli: Compt. rend. Soc. Bid., **88,** 400, 1923.		36	M.	10 yrs.		
18.	Rikl: Zentralbl. f. allg. Path. u. path. Anat., **35,** 5, 310, 1924.		47	M.	2 yrs.		
19.	Askanazy: Quoted by Sternberg, in Henke, Lubarsch Bd. 1, Teil 1, 333.		54	M.			
20.	Houdard, and Huffnagel: Bull. de l'Assn. franc. p. l'étude du Cancer, **16,** 377, 1927.		65	M.			
21.	Spitznagel: Wien. klin. Wchnschr., **42,** 983, 1925.		65	M.			
22.	Spitznagel: Wien. klin. Wchnschr., **42,** 983, 1925.		45	M.			
23.	Carmichael, Davie, and Stewart: Jour. Path. and Bacteriol., **40,** 601. 1935.		63	M.	4 yrs.	Excision Recurrence Reexcision	Recurrence 3 yrs. after first excision. Secondary excision 10 yrs. after first operation. Pt. died soon after of cerebral arteriosclerosis

No.	Source	Patient	Age	Sex	Duration of Symptoms	Treatment	Follow-Up
24.	Carmichael, Davie, and Stewart: Jour. Path. and Bacteriol., **40,** 601, 1935.		58	F.	2½ yrs.	Excision	
25.	Carmichael, Davie, and Stewart: Jour. Path. and Bacteriol., **40,** 601, 1935.		47	M.	2 yrs.	Excision	
26.	Carmichael, Davie, and Stewart: Jour. Path. and Bacteriol., **40,** 601, 1935.		58	M.	30 yrs., with increase in size during last 3 yrs.	Excision	No recurrence after 2 yrs.
27.	Carmichael, Davie, and Stewart: Jour. Path. and Bacteriol., **40,** 601, 1935.		58	M.	10 mos.	Excision	No recurrence after 1 yr.
28.	Carmichael, Davie, and Stewart: Jour. Path. and Bacteriol., **40,** 601, 1935.		92	M.	15 yrs.	Excision	No recurrence after 6 mos.
29.	Carmichael, Davie, and Stewart: Jour. Path. and Bacteriol., **40,** 601, 1935.		66	F.	3 mos.	Excision	
30.	Carmichael, Davie, and Stewart: Jour. Path. and Bacteriol., **40,** 601, 1935.		76	F.	2½ yrs.	Excision	
31.	Ssobolew: Frankfurt. Ztschr. f. Path., **11,** 462, 1912.		54	M.	5 mos.		Letter returned undelivered
32.	Ssobolew: Frankfurt. Ztschr. f. Path., **11,** 462, 1912.		"Middle-aged"	M.			"Malignant in part"
33.	Feldman: Zentralbl. f. allg. Path. u. path. Anat., **27,** 25, 1916.		51	M.	8½ yrs.		
34.	Nicholson, G. W.: Guy's Hosp. Rep., **73,** 37, 1923.		60	F.	"Few mos."	Excision	Patient of Sir R. Luce, retired. Records not available at Guy's Hospital
35.	Nicholson, G. W.: Guy's Hosp. Rep., **73,** 37, 1923.		50	M.	1 or 2 yrs.	Excision	Guy's Hospital records not available now
36.	Stöhr, Risak: Arch. f. klin. Chir., **143,** 609, 1926.	Franz Str. Pr. Nr. 734/1925	2½	M.	8 wks.	Excision	Malignant
37.	Letulle: Bull. de l'Assn. franc. p. l'étude du Cancer, **16,** 380, 1927.		Adult	M.			
38.	Bottin: Bull. de l'Assn. franc. p. l'étude du Cancer, **18,** 819, 1929.		56	M.	1 yr.		
39.	Brachetto-Brian: Bol. y trab. de la Soc. de cir. de Buenos Aires.		57	M.	1 yr.	Excision	Well. No recurrence after 10½ yrs.
40.	Hamperl: Virch. Arch. f. path. Anat., **282,** 724, 1931.		70	M.			
41.	Hall, E. M.: Arch. Path., **19,** 756, 1935.		48	M.	1 yr.	Excision	Well. No recurrence after 6½ yrs.
42.	Harris, P. N.: Am. Jour. Path., **13,** 81, 1937.		61	M.		Excision	Well. No recurrence 2 yrs. later
43.	Harris, P. N.: Am. Jour. Path., **13,** 81, 1937.		62	M.	4 yrs.	Excision	Well. No recurrence 5 yrs. later

TABLE IV—(*Continued*)

No.	Source	Patient	Age	Sex	Duration of Symptoms	Treatment	Follow-Up
44.	Wendel, A., Jr.: Jour. Cancer Res., **14,** 123, 1930		56	M.	1½ yrs.	Excision	No recurrence 10 yrs. later. Died of "heart trouble"
45.	Cunningham, W. F.: ANNALS OF SURGERY, **90,** 114, 1929.	Hist. No. 6911 Bellevue Hosp. N. Y. C.	16		3 yrs.	Excision	"Record can't be located"
46.	Wood, D. A.: Am. Jour. Path., **11,** 889, 1935.		37	M.			
47.	Wood, D. A.: Am. Jour. Path., **11,** 889, 1935.		48	M.			
48.	Wood, D. A.: Am. Jour. Path., **11,** 889, 1935.		71	M.			
	16 PREVIOUSLY UNREPORTED CASES						
49.	Memorial Hospital* records, 1915–1941	B. R. 57792—1939	54	M.	1 yr.	Excision	No recurrence 1 yr., 8 mos. later. Also has reticulum cell lymphosarcomatosis
50.	Memorial Hospital* records, 1915–1941	G. E. M. 49561—1935	47	M.	1 yr.	Excision	No recurrence after 1 mo.
51.	Memorial Hospital* records, 1915–1941	I. I. 53504—1937	41	M.	6 mos.	Excision	Fails to respond to follow-up requests
52.	Memorial Hospital* records, 1915–1941	E. C. 56329—1938	8½	F.	1 yr.	Excised. Keloid of scar later treated with radon bulb	No recurrence after 2 yrs., 4 mos.
53.	Memorial Hospital* records, 1915–1941	W.K. 53265—1937	51	M.	10 mos.	Excision	No recurrence after 3 yrs., 8 mos.
54.	Memorial Hospital* records, 1915–1941	J. L. 59329—1940	53	M.	6 mos.	Excision	No recurrence after 1 yr.
55.	Memorial Hospital* records, 1915–1941	J. L. 57840—1939	64	M.	3 mos.	Excision; followed by x-ray	See text. Tumor "hardly palpable" after 1 yr.
56.	Memorial Hospital* records, 1915–1941	E. M. 60724—1940	69	M.	3 yrs.	Excision	No recurrence after 3 mos.
57.	Memorial Hospital* records, 1915–1941	C. O. 58899—1940	58	M.	3 yrs.	Excision	No recurrence after 1 yr., 2 mos.
58.	Memorial Hospital* records, 1915–1941	G. K. 49973—1935	36	F.	1 yr.	Excision	No recurrence after 5 yrs., 9 mos.
59.	Oughterson, A. W.* New Haven Hospital	B18276	53	M.	3 to 4 yrs.	Excision (bilateral)	Too recent
60.	Stout and Fabro* Presbyterian Hosp., N. Y. C.	Hist. No. 260904 Path. No. 61427	51	M.	1 yr.	Excision	No recurrence after 4 yrs.
61.	Stout and Fabro* Presbyterian Hosp., N. Y. C.	Hist. No. 418878 Path. No. 54494	55	F.	1 yr.	Excision; followed by x-ray for keloid	No recurrence after 5 yrs.

* I am indebted to Drs. A. W. Oughterson, Arthur Purdy Stout, J. Alfred Fabro, and Hayes Martin for permission to include the data on these cases.

No.	Source	Patient	Age	Sex	Duration of Symptoms	Treatment	Follow-Up
62.	Stout and Fabro* Presbyterian Hosp., N. Y. C.	Surg. Path. No. 14010	54	M.	1½ yrs.	Biopsy	Died of pneumonia 1 yr. after biopsy. Tumor had grown "only slightly"
63.	Stout and Fabro* Presbyterian Hosp., N. Y. C.	Surg. Path. No. 13751	61	M.	6 mos.	Excision	None
64.	Stout and Fabro* Presbyterian Hosp., N .Y. C.	Surg. Path. No. 15811				Excision	No recurrence after 2 yrs.

Prognosis.—From the information at hand, adenolymphoma is a benign tumor (with rare exceptions) which, when adequately excised, usually does not recur.

Added to the 64 cases analyzed above are three others. Although, histologically, they differ slightly from the usual picture, they undoubtedly belong to the same group of neoplasms. Clinically, they behave in an identical manner:

CASE REPORTS

Case 1.—New Haven Hospital No. B7034; Path. No. 23559: A white male, age 59, was referred to the hospital, July 24, 1940, by Doctor Brown, of Danbury. Eleven months previously a mass appeared in the region of the left parotid gland. This seemed to diminish in size after extraction of a diseased tooth, then renewed its former slow growth. In the two weeks before admission the mass grew more rapidly.

Examination showed a firm, nontender mass behind the angle of the jaw, measuring 2×2.5 cm. There was a tongue-like projection around the ramus of the mandible. There were no other pertinent findings. A "metastatic series" of roentgenograms failed to show any other tumors. R.B.C. 5,500,000; W.B.C. 10,850, with a normal differential distribution. Hemoglobin was 16 Gm. On July 30, 1940, the mass was excised under local novocain anesthesia. At operation, no distinct capsule was grossly observed between the parotid gland and the tumor, and the lower portion of the gland was excised, including the neoplasm.

Postoperatively, a small salivary sinus tract drained for about three weeks. This healed quickly. The patient is being followed in the Tumor Clinic. When last seen, over a year since the excision, there was no recurrence.

Case 2.†—Mount Sinai Hospital, New York, Path. No. 18718: A white male, age 53, had had a swelling in the left parotid region for four years. The tumor was completely removed surgically. There was no postoperative radiation. Six months after the excision there was no recurrence.

Case 3.‡—Mount Sinai Hospital, New York, Path. No. 18753: A male, age 50, had noted a tumor in the region of the left parotid gland for about two years prior to seeking therapy. The mass was excised, but since the surgeon did not believe all the tumor was removed, he implanted radium as follows: At upper angle of wound, 19.8 mg. (1.0 Mm. platinum) 1.1 cm. active length for 24 hours. Total 475.2 mg. hours. At lower angle of wound, the same factors and dosage. Total 475.2 mg. hours. Postoperatively, he was given roentgenotherapy. Dosage 325 r. in four divided doses (200 K.V., 1 Mm. Cu). This case is too recent to report a follow-up.

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* I am indebted to Drs. A. W. Oughterson, Arthur Purdy Stout, J. Alfred Fabro, and Hayes Martin for permission to include the data on these cases.

† I am indebted to Drs. Paul Klemperer and John Garlock for permission to report this case.

‡ I wish to thank Drs. Paul Klemperer and Ralph Colp for permission to include this case.

Microscopically, these three tumors are strikingly similar to each other. Like the usual form of adenolymphoma they contain a matrix of lymphoid tissue (Fig. 2). In areas, this consists of diffuse lymphocytic infiltration. Elsewhere, there are aggregates resembling germinal centers. In the center

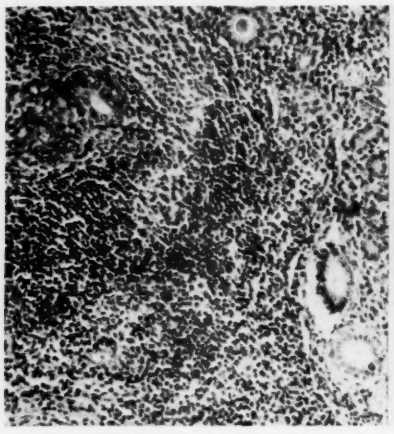

FIG. 2.—Tumor in Case 1: Compare with Figure 3. (×300)

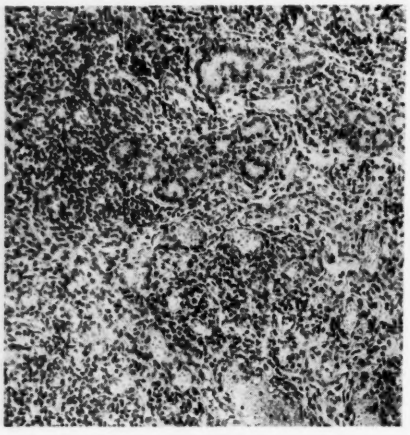

FIG. 3.—Lymph node adjacent to parotid gland. Newborn infant. (×200)

of the latter are groups of large cells which resemble epithelioid cells rather than young lymphocytes. Here and there are many small cysts lined with low cylindrical cells with vesicular nuclei. Between the bases of these are small cuboidal cells, irregularly spaced. The cysts contain a pale pink, homogeneous material, cellular debris, and occasionally cholesterol crystals. In addition to the small cysts, and scattered in the lymphoid matrix, are other epithelial cells, singly and in strands. In places the tumor is separated from the parotid gland by a thin, fibrous capsule. Elsewhere, there is no capsule and the tumor infiltrates the glandular parenchyma.

Pathologically, all of these tumors resemble that described recently by Fein,[4] classified by him as lympho-epithelioma.

Histogenesis.—The theories concerning the origin of adenolymphomata have been thoroughly presented by Jaffé,[6] Stout and Kraissl,[13] Freshman and Kurland,[3] Albrecht and Artz,[1] Hamperl,[5] Warthin,[14] and others. The reader is referred to these authors for a complete discussion.

The presence of parotid ducts and acini within the surrounding lymph nodes has been described by R. Neisse,[8] and G. W. Nicholson.[9] Neisse, who studied these structures in fetuses as well as newborn infants, felt that the parotid tissue became included in the lymph nodes as a result of the growth and development of the nodes from small patches of lymphocytes which had previously surrounded the parotid tissue. He found undeveloped parotid structures directly adjacent to lymphocytic tissue in the 9-cm. fetuses, and lying within the nodes themselves in fetuses measuring 12 cm. and larger.

Drs. Henry Bunting* and Robert Tennant, Department of Surgical

*I wish to thank Doctor Bunting, particularly, for his help here.

Pathology, Yale School of Medicine, repeated the investigation. They studied the lymph nodes adjacent to the parotid gland in two prematures and five full term, stillborn infants. In three of this group small acinar structures and ducts typical of the parotid were found within these lymph nodes (Fig. 3). In most instances, these glandular structures were situated in the hilar regions of the nodes (a fact also noted by Neisse and by Nicholson).

From the similarity of the structure of the three tumors described above to that of this common finding in newborn infants, it seems probable that such tumors have arisen from the subsequent growth of such parotid tubules and acini as have been included within lymph nodes.

CONCLUSIONS

Adenolymphoma of the parotid region is an unusual salivary gland tumor. It probably comprises considerably less than 10 per cent of all parotid tumors. Were complete figures known, this ratio would presumably fall lower. It occurs at all ages, but predominantly in the fifth, sixth, and seventh decades. The life history is that of a slow growing tumor, which is relatively asymptomatic. The tumor is usually present for many months before attention is sought. It occurs five times oftener in men than in women. Surgical excision is the treatment of choice. Since the capsule is not always complete, the tumor should be meticulously dissected out, rather than enucleated. When completely excised, the tumor rarely has been known to recur. Histologically, it is benign. A discussion is appended concerning the possible histogenesis of adenolymphomata. Three cases are reported of a clinically identical and histologically similar tumor, which the author believes belong to the same group.

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ADRENALIN-PRODUCING PHEOCHROMOCYTOMA OF THE ADRENAL ASSOCIATED WITH HYPERTENSION

REPORT OF THREE CASES

JACK D. KIRSHBAUM, M.D., AND RUTH B. BALKIN, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF PATHOLOGY, WOODLAWN HOSPITAL; THE COOK COUNTY HOSPITAL, AND THE DIVISION OF SURGERY NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILL.

THE TERM PHEOCHROMOCYTOMA is restricted to-day to those tumors that arise from the adrenal medulla, whereas the term paraganglioma connotes a tumor that originates in the chromaffin system exclusive of the adrenal gland. Pheochromocytomata are characterized chiefly by the markedly increased production of adrenalin, which, according to Ewing,[1] occurs only in the benign forms. These tumors are usually benign and the diagnosis of malignancy can only be made on histologic examination of the tumor and not on the clinical findings. Surgical removal of the tumor usually results in relief of the hypertension.

Grossly, these tumors are moderately firm, and vary in size from that of a pinhead to the size of a fetal head and have been reported to weigh up to 2,000 Gm. Microscopically, these tumors form small groups of cells or show a diffuse growth of polygonal, oval, or round cells. Giant cells are usually present, may be either mononuclear or multinuclear, and often resemble ganglion cells. The stroma which is fibrillar and forms narrow trabeculae contain numerous blood vessels. Hemorrhage, necrosis, and cystic degeneration frequently occur.

In a review of the literature of pheochromocytomata, Brunschwig and Humphreys[2] collected 103 cases, up to 1939. Since then, ten additional cases have been reported. We wish to report three cases of adrenalin-producing pheochromocytoma of the adrenal, from a series of 14,437 consecutive autopsies performed at the Cook County Hospital, from 1929 to March, 1941, inclusive. Of the total group reported to date, there have been 18 cases that have come to surgery, and in those that survived there was a marked permanent drop in blood pressure. A biologic assay of the tumor was performed in only 13 cases from both surgical and autopsy sources. In some instances the assay was qualitative, but in the majority it was quantitative. In one case the authors were able to demonstrate the presence of an increased amount of adrenalin in the blood during an attack.[3] The adrenalin content of the tumors examined has varied from 1 to 40 mg. per Gm. of tumor tissue. One of our cases contained 4.15 mg. of adrenalin per Gm. of tissue; while, in another, qualitative tests, only, were performed.

The majority of the cases of pheochromocytoma have been encountered in necropsy material, and it is only since 1929, following the report of Rabin,[4] that clinicians have made the diagnosis during life. The clinical diagnosis is

usually made on the basis of paroxysmal hypertension, and some of the accompanying symptoms and findings such as glycosuria, vasomotor pallor followed by flushing, headache, nausea, and vomiting, dyspnea, feeling of suffocation, pulmonary edema, and great susceptibility to surgical shock, even during minor surgical procedures. Tachycardia may also be present, although, with the rise in blood pressure, the pulse may become slow and bounding.

In view of the above discussion, it might be well to mention that there are cases of paroxysmal hypertension which have been operated upon with the diagnosis of pheochromocytoma of the adrenal when, at operation, no tumor was found. Recently, one of us (J. D. K.) saw a patient, a female, age 38, operated upon for a suspected pheochromocytoma. Examination of the surgically removed tumor (Fig. 9) revealed a cyst of the adrenal which, when assayed, contained no adrenalin. Removal of the tumor has produced no fall in blood pressure. One year after operation the blood pressure has varied from 190 to 210 systolic and 60 to 90 diastolic.

CASE REPORTS

Case 1.—White, male, age 28, entered the Cook County Hospital, December 15, 1940, in a comatose condition. The history was elicited from the mother, who stated that the onset was characterized by a severe headache that started two days before admission, and lasted through the following day. On the day following the onset, he vomited twice and felt better. That night he lapsed into coma. A diagnosis of meningitis was made, and hospitalization advised. The mother stated that the patient had been perfectly well before the acute episode, with the exception of his having had measles in childhood. He had, also, had an operation for congenital cataract, which had resulted in an improvement in his vision.

Physical examination revealed a comatose, white male who was very restless, and who was breathing stertorously. Temperature 104.2° F., pulse 200, blood pressure 230/70. The neck showed a slight rigidity. There was a systolic murmur at the apex. No râles were heard in the lungs. The only other findings of significance were positive Kernig and Brudzinski signs. The spinal fluid was under slightly increased pressure, and was turbid. The Pandy test was 4 plus, the cell count showed 1,090 cells, all polymorphonuclear leukocytes, and, on smear, pneumococci, Type 18, were seen. The impression was that the patient had a Type 18 pneumococcic meningitis and an auricular tachycardia. The patient was given sodium sulfapyridine and 360,000 units of pneumococcic antiserum, intravenously. In spite of this therapy his course was rapidly downhill, and the patient expired 15 hours after admission to the hospital.

Autopsy.—The body was that of a well-developed, well-nourished, white male. The left pupil was larger than the right. The pleural cavities were free. The pericardial sac contained 20 cc. of a clear straw-colored fluid. The heart weighed 520 Gm. The myocardium was very firm and light brown-red. The wall of the left ventricle measured 22 Mm. in thickness, and the right ventricle was 5 Mm. thick. The aorta and the bases of the leaflets of both the aortic and mitral valves showed numerous fatty and hyaline plaques. Both coronary arteries showed a moderate sclerosis and a narrowing of the lumina. The lungs revealed a hemorrhagic bronchopneumonia in all the lobes. The thyroid weighed 12 Gm., and was rich in colloid. The liver was enlarged and weighed 2,020 Gm. The spleen weighed 55 Gm. and showed a marked infectious softening. The pancreas weighed 85 Gm., and was soft. The kidneys, together, weighed 350 Gm. and showed a marked congestion. The brain was swollen and, on the surface, especially over the cerebellum, there were small accumulations of a greenish purulent material.

The left adrenal weighed 73 Gm. (Fig. 1), and was moderately firm. On the surface along one edge there were islands of compressed cortical tissue. For the most part, the mass was encapsulated, firm, and, on section, measured 85x55x40 Mm. The sectioned surface of the mass appeared light grayish-brown. At the periphery it was slightly lighter, while the central portion was occupied by a 20x25 Mm. light yellow-green translucent area. Fixation of a portion of the tumor in potassium bichromate solution caused the surface to turn deep brown. The right adrenal weighed 10 Gm., and appeared normal.

Microscopic Examination.—This revealed the tumor to be composed of large polygonal cells arranged in alveoli. The cells contained oval to round nuclei, in which were included a finely granular chromatin (Fig. 2). In the cytoplasm, particularly in the sections previously fixed in chromate, a fine reddish-brown pigment was present. The nuclei, for the most part, were small; however, many were very large, occasionally

FIG. 1.—Case 1: Photograph shows the large pheochromocytoma in the left adrenal. Note the compressed, intact adrenal tissue in the periphery.

of bizarre shape or multinucleated (Fig. 3). No mitotic figures were seen. Mallory's stain revealed fine strands of connective tissue between the cells, and the alveoli were separated by narrow trabeculae that often contained blood vessels (Fig. 4). Throughout the tumor, but chiefly in the central portion there were extravasations of blood and areas of cystic degeneration. At the periphery of the tumor there was a narrow rim of intact but compressed cortex. Several islands of cortical cells were isolated beneath the capsule of the tumor (Fig. 5).

When stained with Sudan III, little fat was seen, and what was present was in the form of coarse fat droplets.

Anatomic Diagnosis.—Pneumococcic meningitis (Type 18); pheochromocytoma of the left adrenal; marked hypertrophy of the heart; marked arteriosclerosis of the coronary arteries, the aorta and cerebral vessels; hemorrhagic bronchopneumonia of both lungs; marked fatty changes of the liver and passive congestion of the kidneys.

Bio-assay of Adrenalin Content in the Tumor.—Eight grams of the adrenal tumor were submitted to Dr. H. A. McGuigan, of the Department of Pharmacology of the University of Illinois Medical School. The tissue was ground up and extracted with 50 cc. of N/10 hydrochloric acid. It was placed in the icebox for 24 hours and re-extracted with 50 cc. N/10 hydrochloric acid, filtered and neutralized with sodium carbonate and made up to 500 cc. A male dog, that weighed 12.3 Kg. was anesthetized with nembutal. When 0.6 cc. of the extract was injected intravenously, a rise in blood

pressure, equal to that produced by the injection of 1 cc. of a 1:25,000 solution of adrenalin, was obtained (Graph 1). Eight grams of tumor yielded 33.2 mg. of adrenalin, and the entire tumor yielded approximately 303 mg. of adrenalin, or 0.31 per cent.

Case 2.—White, male, age 53, was admitted to Cook County Hospital, November, 1934, in coma. The temperature was 103.6° F.; blood pressure 230/170. No history was available except for a roentgenologic report in his pocket, which stated that the

FIG. 2. FIG. 3.

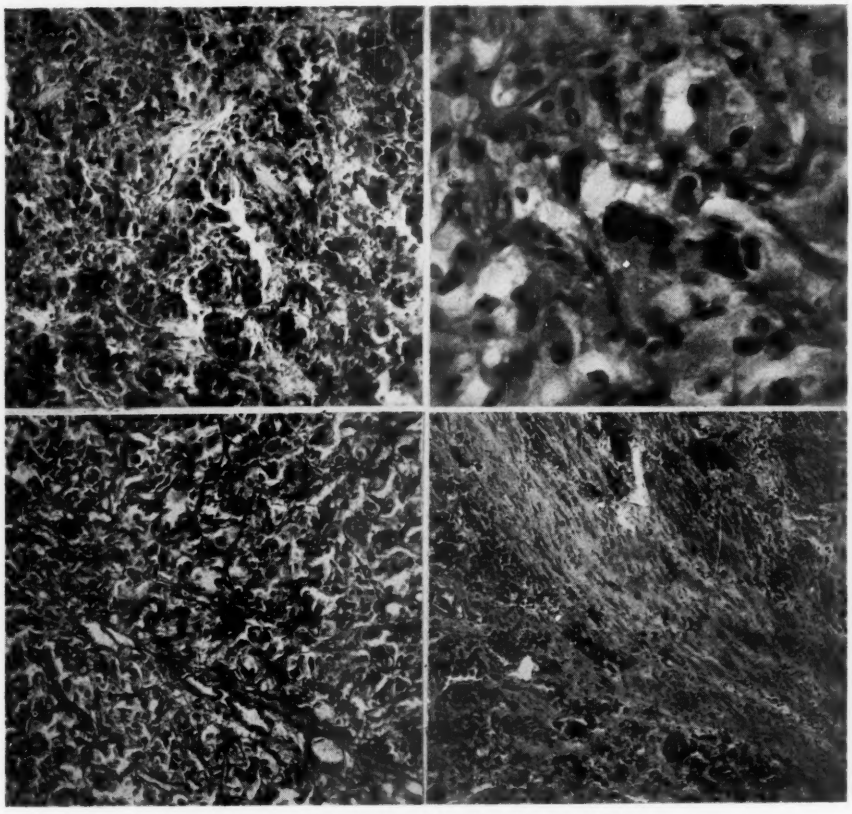


FIG. 4. FIG. 5.

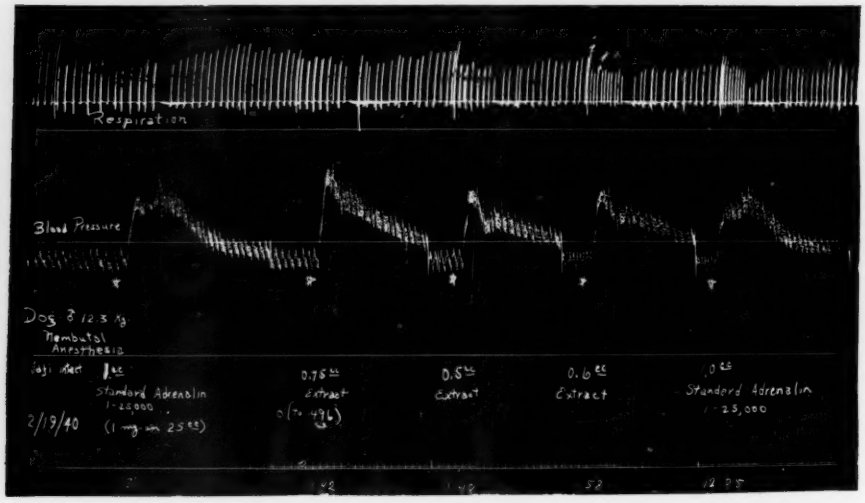
FIG. 2.—Case 1: Low power magnification showing the alveolar arrangement of the cells.
FIG. 3.—Case 1: High power magnification. Note the bizarre-shaped giant cells resembling ganglion cells.
FIG. 4.—Case 1: Photomicrograph showing the fine trabeculae between the groups of cells. (Mallory's phosphotungstic, hematoxylin.)
FIG. 5.—Case 1: Photomicrograph showing the capsule about the tumor, with islands of adrenal tissue in the periphery.

patient may have had a tumor of the lung. He was having Cheyne-Stoke's respirations, and before the examination could be completed, the patient expired.

Necropsy.—This disclosed a spontaneous hemorrhage in the right cerebellar hemisphere as the immediate cause of death. The left adrenal was transformed into a mass 10x8.5x8 cm. (Fig. 6). It was encapsulated and moderately firm. On section, it was light brown, and contained several cystic areas that measured up to 25 Mm. in diameter. Histologically, this tumor resembled the one previously described (Case 1), except that the trabeculae were coarser and often isolated small groups of cells (Fig. 7). In addition to the above findings, there were many pinhead, up to 2 cm. in diameter, sub-

cutaneous nodules and areas of pale brown pigmentation over the trunk, neck, and extremities. There was also a goose egg-sized, semifirm mass in the right third interspace, which was attached to the intercostal nerve. There was, also, a small, solitary neurofibroma in the submucosa of the stomach.

Anatomic Diagnosis.—Massive, spontaneous cerebellar hemorrhage; benign pheochromocytoma of the left adrenal; multiple neurofibromata in the skin; single neurofibroma in the stomach, and in the right third intercostal space.



GRAPH 1.—Case 1: Photograph of the tracing showing the effects of injecting an extract of tumor tissue into a dog. Note the prompt rise in blood pressure.

Case 3.—Previously reported by Ford K. Hick[5]: White, female, age 64, was brought to Cook County Hospital in a stuporous state, and died a few hours later. It was learned from a son that the patient had slept much of the time during the day for the past few weeks.

Physical examination disclosed an obese, white female; blood pressure 180/105. The pupils were unequal. *Clinical Diagnosis:* Cerebral hemorrhage.

Autopsy.—The essential anatomic findings were a pea-sized aneurysm of the anterior communicating cerebral artery, with rupture, and severe subarachnoid hemorrhage. Attached to the left adrenal gland was an encapsulated, soft egg-shaped mass, measuring 4x2x2 cm. (Fig. 8). Histologically, this tumor resembled the two preceding cases (Cases 1 and 2).

Anatomic Diagnosis.—Ruptured aneurysm of the anterior communicating cerebral artery, with extensive intra- and extrameningeal hemorrhage at the base of the brain; pheochromocytoma in the region of the left suprarenal gland.

When an extract of a gram of tumor tissue was injected into a dog, it produced a marked rise in blood pressure. No quantitative determination of the adrenalin content of the tumor was made.

COMMENT.—Our first case is unique in that it occurred in a young male, age 28, who, at autopsy, showed the effects of a long-standing hypertension, such as the marked enlargement of the heart and arteriosclerosis, but without pathologic changes in the kidneys. As far as could be learned from the past history, there was no evidence that the patient may have had a paroxys-

mal type of hypertension. Thus, one might suggest that the secretion of adrenalin from the tumor was continuous rather than intermittent.

The second case is one of the few reported in which there is a coincident neurofibromatosis. In 1938, Brenner, Konzett and Nagl[6] reviewed the literature and, out of 64 cases of pheochromocytoma, reported they were able

FIG. 6.—Case 2: Photograph of a pheochromocytoma of the left adrenal. Note areas of cystic degeneration.

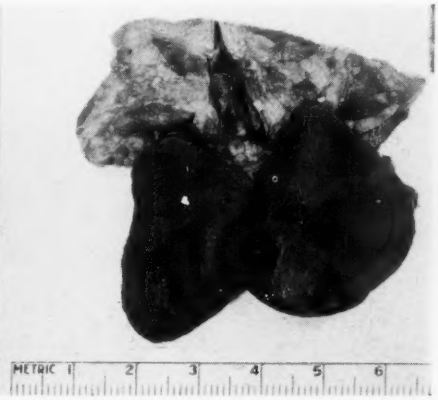


FIG. 7.—Case 2: Photograph showing the tumor attached to the left adrenal, with central, cystic degeneration.

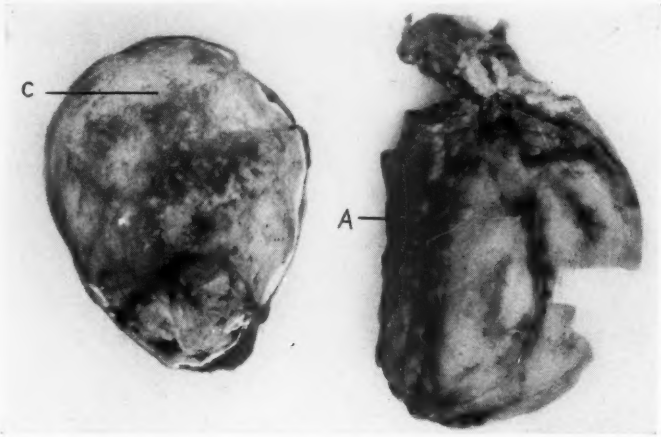


FIG. 8.—Case 3: Photograph showing a large cyst of the adrenal. Note (A) islands of adrenal tissue on the surface of the tumor. (C) Plaques of calcium lining the thin-walled cyst. This patient had a paroxysmal type of hypertension which was unrelieved following surgical removal of the tumor.

to find only eight cases in which these two pathologic processes occurred concomitantly. The third case was peculiar in that the tumor was outside but attached to the adrenal. Hick[5] believed that the tumor had its origin in the medulla, and, as it grew, it became separated from the adrenal.

Two of the three cases here presented were males, and the third was a female. The age incidence ranged from 28 to 64 years. The majority of cases reported occurred in the third and fourth decades, although one of the cases recorded was in a 12-year-old girl. The majority of these tumors

are unilateral; however, Brunschwig and Humphreys[2] noted 13 instances of bilateral involvement.

SUMMARY

Three cases of pheochromocytoma of the adrenal are here presented. One of these tumors was situated outside of the adrenal, but was attached to it. Two occurred in males (28 and 53 years of age), and the third, in a female (age 64).

All three tumors were benign, and were incidental findings at necropsy.

Hypertension was present in all three cases and the systolic pressures ranged from 180 to 230 Mm.Hg.

Two of the three cases (Cases 1 and 3), when assayed, revealed an adrenalin-producing substance. In Case 1, 73.0 Gm. of tumor tissue yielded approximately 303 mg. of adrenalin.

Arteriosclerosis was a prominent feature in all the cases, and the heart was hypertrophied in all.

Neurofibromatosis may be associated with pheochromocytoma, as it was in one of the cases.

A case of a calcified cyst of the adrenal in a woman, age 38, who had developed a sudden hypertension, and was not relieved of her high blood pressure subsequent to surgical extirpation of the tumor, is cited.

A total of 116 cases of pheochromocytoma of the adrenal, from both surgical and necropsy sources, have thus far been reported.

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PHEOCHROMOCYTOMA WITH HYPERMETABOLISM

REPORT OF TWO CASES

E. PERRY MCCULLAGH, M.D., AND W. J. ENGEL, M.D.

CLEVELAND CLINIC

CLEVELAND, OHIO

THE CLINICAL SYNDROME associated with pheochrome tumors of the adrenal medulla has come to be a well recognized entity and a number of cases have been reported, some of which have been relieved by surgical removal of the tumor. Although paroxysmal hypertension has frequently been noted, it is not a *sine qua non* in the diagnosis. In our two cases persistent hypertension developed. Variations in blood pressure were present early in the course of observation in the first case and these persisted and were superimposed upon the constant hypertension in the second case. One of our cases was correctly diagnosed before operation and was cured by surgical removal of the tumor, while the second is from our records and was diagnosed at autopsy, having been considered clinically to be hyperthyroidism. Hypermetabolism was an outstanding feature in both cases.

Until the past decade, the vast majority of these tumors were found at autopsy and reported by pathologists. Brunschwig and Humphreys[1] found 103 cases in the literature to 1940. These were mostly found at autopsy. McKenzie and MacEachern[2] presented an excellent paper in 1938, at which time they had collected 20 cases treated surgically. Since that time several additional surgical cases have been reported. Although the tumor is still uncommon, it is being recognized and properly treated much more frequently now than it was previously.

CASE REPORTS

Case 1.—A 19-year-old girl student was referred to one of us (E. P. McC.) on June 12, 1939, with the following history: On December 24, 1937, she was knocked down by an automobile. She was not badly hurt, although roentgenologic examination the following day disclosed three fractured ribs on the right side. During the following year she tired readily, and was not strong enough to attend school, her illness confining her to bed for a week or two at a time during 1938. There was some loss of weight, although she ate and slept well. The family physician found that she had some hypertension. She then consulted another physician who checked her blood pressure very carefully and told her that there was absolutely no elevation and that she should forget about it. The family physician, not being satisfied with this, urged consultation with a third physician, who found a definite hypertension. This experience caused the family to lose faith in the second physician who was an exceedingly capable man, and this was restored only after it was explained that they all were correct.

During the six months preceding our examination, in addition to weakness, she complained of "spells" which occurred 15 to 20 times a day. In a typical attack the patient first experienced a sense of intense heat occurring first over the face, and then extending over the entire body. This was occasionally associated with momentary dizziness and faintness. Almost immediately after the sensation of heat a profuse, drenching

perspiration began which also started on the face and spread from there over the body. The hands and feet did not participate in this hyperhydrosis and usually felt cold and clammy. With the spells she always experienced palpitation of the heart with increased precordial activity, and could feel the pounding in the abdominal aorta. With these attacks she felt trembly and often her whole body shook. The spells lasted a few minutes, and when frequent, one merged into the next. They occurred at any time of the day or night and were never precipitated in any constant manner, often occurring when she was apparently at complete rest. Between spells there was weakness but no other outstanding symptoms.

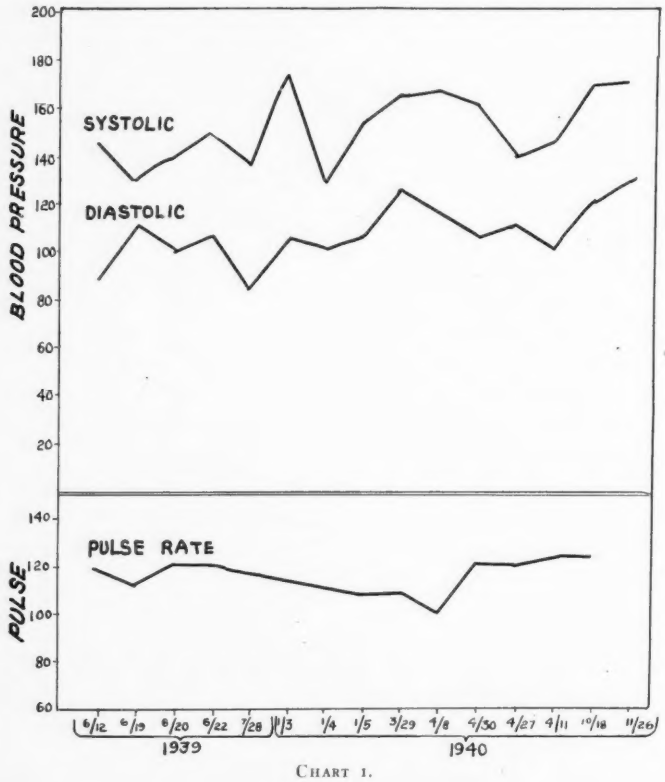

CHART 1.

Physical Examination.—The patient was an asthenic, tired looking young woman. Weight 111 pounds (50.5 Kg.); pulse 120; blood pressure 152/100. The eyes were normal and there was no exophthalmos. The thyroid was palpable but not enlarged. The chest and lungs were normal. A medium-grade digital tremor was present. Complete neurologic examination showed no other abnormalities.

Laboratory Data.—Urinalysis showed the p_H of the urine to be 5.2, the specific gravity 1.020, with a trace of albumin, and no sugar. Microscopic examination showed rare red blood cells and one to two white blood cells per high power field. The fasting blood sugar was 95 mg., blood urea 30 mg., and cholesterol 139 mg. per cent. Wassermann and Kahn tests negative. On June 19, 1939, the urea clearance test showed 147 per cent the first hour, 125 per cent the second hour. On December 9, 1940, the urea clearance test showed 140 per cent the first hour, 130 per cent the second hour, and the

blood urea was 33 mg. per 100 cc. The glucose tolerance, using 100 Gm. of glucose by the oral single dose method, October 11, 1940, showed the following blood sugar levels:

Hour:	Fasting	½	1	2	3	4
Blood sugar:	128	267	254	75	45	76

Although diabetes was not present, it is interesting to compare this with the same test done postoperatively, January 31, 1941. There had been a definite fall in blood sugar levels at that time. The test was as follows:

Hour:	Fasting	½	1	2	3	4
Blood sugar:	88	168	168	108	49	72

Although it was not suspected that adrenal cortical sex hormones would be at abnormal levels, these were determined. The androgens, by the capon comb-growth method of McCullagh and McLin,[3] were 11 I.U. in a 24-hour specimen.* Seventeen-ketosteroids,

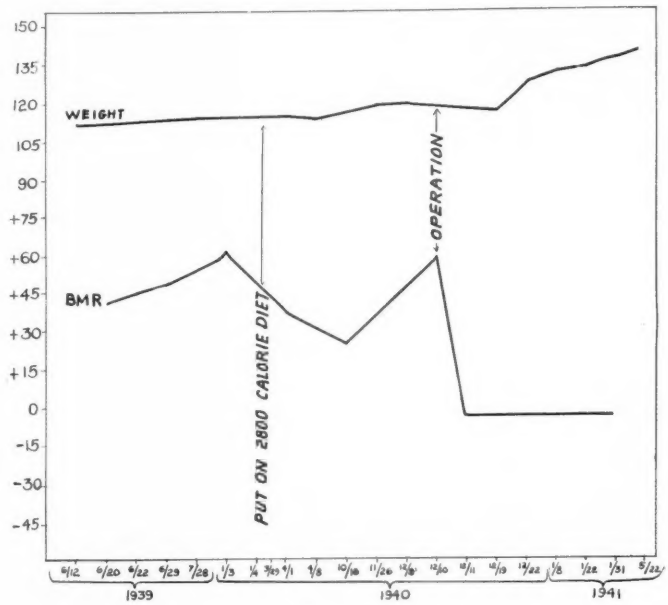

CHART 2.

estimated by the electric colorimeter by a modification of the Callow method, showed 28 colorimetric units, which is normal.

Following the first examination and reports, the impression was either neurocirculatory asthenia or adrenal sympathetic syndrome, as in pheochromocytoma.

For further investigation, she was referred to the Department of Urology, June 23, 1939. Cystoscopic examination revealed a normal bladder. Ureteral catheters were passed and separate kidney urines were normal. The bilateral pyelogram showed normal kidney pelves and neither kidney was displaced. No tumor shadow could be seen in the suprarenal area. Perirenal air injection was suggested and carried out, June 28, 1939. However, before the requisite amount of air could be injected, the patient became dyspneic, suffered mild collapse, and the injection was discontinued. Roentgenograms made at the time and again the following day were of no assistance in diagnosis, as there was insufficient air in the tissues.

We were, therefore, unable to establish a definite diagnosis of adrenal tumor, so the

* Normal for women approximately 10 to 50 international units.

patient continued under the observation of one of us (E. P. McC.). She continued to have the spells of weakness, profuse sweating, and fatigue, although there was little change in her general appearance or condition for the next 18 months. The blood pressure, although variable, was elevated for the most part, and she was never observed to have what we considered to be true paroxysms of hypertension (Chart 1). Even with her spells, the blood pressure was recorded no higher than occasionally at other times. There was persistent tachycardia, and repeated determinations of the basal metabolic rate showed a constant hypermetabolism (Chart 2). In spite of this she never was considered to be a case of hyperthyroidism and the surgical consultant shared this opinion.

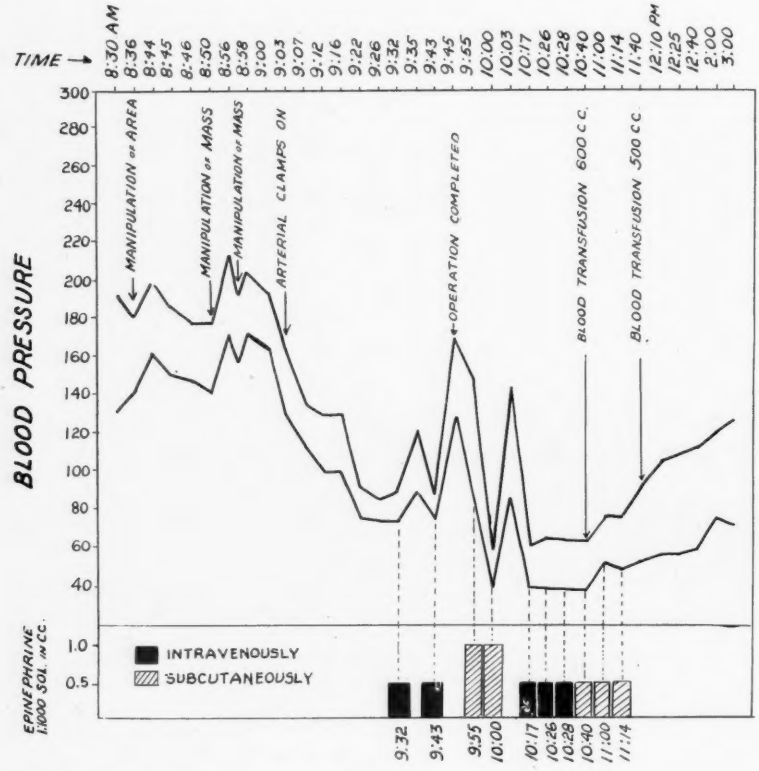

CHART 3.

Throughout this period of observation the clinical diagnosis was probable pheochromocytoma. In October, 1940, an intravenous urogram was made, but we were still unable to demonstrate any displacement of either kidney, and there was no tumor shadow in either suprarenal area. On clinical evidence, however, adrenal exploration was advised, and the patient returned for operation in December, 1940.

The patient was prepared for bilateral adrenal exploration after the technic described by Young.[4] We decided to explore the right side first because these tumors are more prevalent on the right side, and also because the right kidney was lower, which made it seem improbable that the tumor was on the left side.

Even before seeing the tumor we were sure of its presence. Constant blood pressure determinations were made during the operation and manipulation in the suprarenal area was followed by rapid rise of systolic and diastolic pressures to alarming levels (Chart 3). When the tumor was exposed, touching it produced extreme elevation of the blood

pressure as high as 170 Mm. diastolic. As dissection of the tumor proceeded we could see that it was separate from the adrenal gland, which was left intact.

As soon as the blood supply to the tumor was interrupted, the blood pressure dropped precipitously. A plasma transfusion was begun and also the administration of epinephrine, which it was necessary to use in repeated, rather large doses to support the circulation. Doses of 0.5–1.0 cc. of 1/1000 solution were given intravenously at intervals of a few minutes whenever the systolic pressure fell below 90 Mm., a total of 6.0 cc. being administered within three hours following severance of the blood supply to the mass. It was interesting to observe that after the first few doses the drug apparently lost its effectiveness and its administration no longer resulted in a significant rise of pressure. Immediately upon completion of the operation, the patient's condition was quite satisfactory

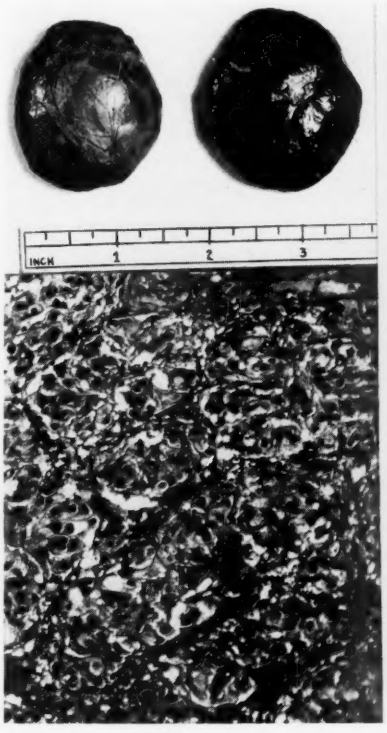

FIG. 1.

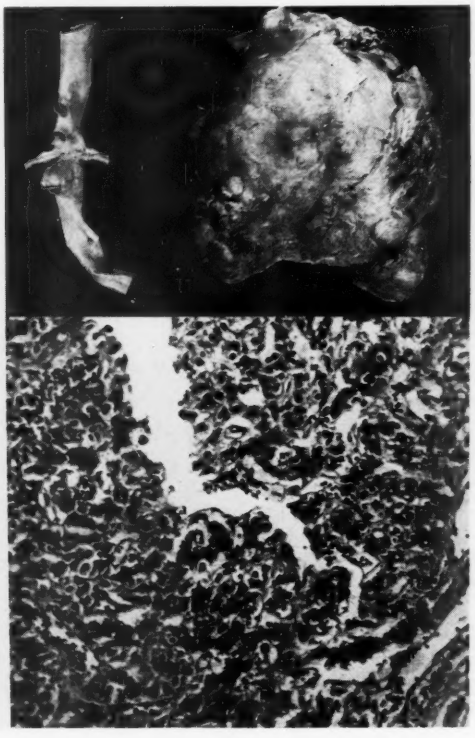

FIG. 2.

FIGS. 1 and 2.—The gross and microscopic appearance of the tumors in Cases 1 and 2, respectively, are shown. The cells of the tumors in each simulate those seen in normal adrenal medulla.

although the blood pressure had not yet risen. Within the next four hours, the patient was given two transfusions of whole blood containing 500 and 600 cc., respectively. By midafternoon of the day of operation the blood pressure had returned to normal, and remained so throughout the remainder of her convalescence.

The great value of transfusion of blood or plasma during and following operation in these cases should be emphasized.

Pathologic Examination.—Dr. Allen Graham: "The specimen consists of a tumor mass (Fig. 1) removed from the right adrenal; it weighs 35 Gm. and measures 5.5x4.3x3.5 cm. It is entirely encapsulated, has a fairly uniform surface, is firm, elastic, and, on section, has a uniform, bulging, homogeneous, yellowish-brown surface. The entire tumor has the color and consistency of adrenal medullary tissue.

"Histologic sections show a very cellular type of tumor consisting of very large irregular cells having an abundance of cytoplasm in which there are many granules. The cells correspond in type to those of the adrenal medulla. The tumor is highly vascularized and has a reticulated stroma." *Pathologic Diagnosis.*—Pheochromocytoma of the right adrenal.

The patient had an uneventful convalescence and was permitted to leave the hospital on the eleventh day following operation. She has remained entirely well and reported for observation six months postoperatively, feeling well and having gained some 20 pounds in weight. She has been completely relieved of her attacks and the blood pressure has remained at normal levels, the highest postoperative determination being 130 Mm. systolic and 70 Mm. diastolic.

The urea clearance test eight months postoperatively showed 85 per cent clearance in each of two hours. The basal metabolic rates were −4 and −6 per cent. The blood pressure was 124 Mm. systolic and 70 Mm. diastolic. At this time she reported that her weight had decreased ten pounds without any effort or dietary restrictions, the appetite apparently having adjusted itself automatically to metabolic needs.

COMMENT.—Several interesting features of this case bear special comment: Although the blood pressure was variable, this variability was never shown to bear any relationship to her symptoms, for it was repeatedly found to be normal during an attack of sweating, and on several occasions was found to be high when she was feeling well and no attack was present. Of interest also is the upward trend of the blood pressure during the one and one-half years she was under observation before operation (Chart 1). At first, normal readings were occasionally obtained; later, the blood pressure was constantly elevated, much as is seen in essential hypertension. The eyegrounds were examined by the ophthalmologist and were reported to show the changes of essential hypertension, Grades I to II. Attempts were made to reproduce her attacks or aggravate her hypertension by manipulation of the adrenal areas and by bending exercises, but these failed. The rapid flow of blood through the tissues is shown here, as in the second case, to be reported, by the very high urea clearance tests which reveal the result of excessive circulation through a normal kidney. This test, in our opinion, is of particular interest in considering the origin of the hypertension.

The spells of weakness and extreme sweating which formed the chief complaints in this case were at first suspected of being of hypoglycemic origin, but no hypoglycemia was found. Neither did she develop any clinical evidence of diabetes. It is noteworthy, nevertheless, that there was a shift in tolerance to glucose which was apparently brought about following the removal of the tumor, showing that some strain on the glucose metabolism did exist.

Throughout the course of the patient's illness she did not exhibit the marked general redness of the skin which is described in Case 2, but her hands did show, on all occasions, a peculiar redness in the same type of glove distribution in which cyanosis appears in neurocirculatory asthenia.

The hypermetabolism is especially worthy of comment. As seen in Chart 2, repeated preoperative determinations of the basal metabolism showed consistent and pronounced elevations. Associated with this the patient had experienced a marked stimulation of her appetite and she was able to maintain

her weight by following a diet approximating 2,800 calories per day. The finding of a rather severe hypermetabolism, naturally, brought the possibility of hyperthyroidism to mind. We felt that this could be excluded by the absence of the typical appearance of hyperthyroidism and of thyroid enlargement and exophthalmos; also a therapeutic trial with Lugol's solution did not alter her clinical state nor affect her basal metabolism. Finally, the proof that the hypermetabolism in this instance was primarily due to the adrenal tumor is produced by the complete return of the metabolic rate to normal after the removal of the mass. Here, then, is hypermetabolism not of thyroid origin, yet this and the following case emphasize the closeness with which pheochromocytoma may simulate hyperthyroidism.

Following operation this patient presented an unusual complaint of cold intolerance. If a cold breeze struck her she would shake perceptibly and on one occasion the shivering continued for most of an hour. This has gradually improved until, eight months postoperatively, it was scarcely noticeable. The only apparent explanation for this is that there was pronounced vasomotor and pilomotor instability from which she required considerable time to recover.

Case 2.—A young married man, age 28, entered the hospital in November, 1937, complaining of a "run-down condition." His symptoms were of recent onset, and for the preceding two weeks he had had little energy, felt nervous, generally weak, and had a tremor of his hands. The symptoms became so severe that he was forced to stop working, and three days before admission he became markedly exhausted. In spite of a fair appetite during the preceding year, he had lost 28 pounds in weight.

For a year the patient had experienced increased frequency of urination and during the past four months this had become more pronounced. He was forced to void almost every hour during the day and four to six times at night. This severe frequency was unaccompanied by any associated symptoms of burning or dysuria, and he seemed to pass a normal amount of urine at each voiding.

Physical Examination.—The patient was a well-developed man, who had an extremely red face, and a very red, deeply fissured tongue. He weighed 122½ pounds (55.7 Kg.). Temperature 101.2° F. (38.5° C.). Pulse 108. Blood pressure 174/104. The thyroid was enlarged and there was an adenoma in the right lobe, measuring approximately 5x4 cm. The chest and lungs revealed no positive findings. There was no percussible enlargement of the heart. The rate was increased and there were occasional extrasystoles, but no murmurs. Palpation of the abdomen revealed no masses or palpable organs. Neurologic examination showed no abnormalities. There was a rather pronounced digital tremor.

Laboratory Data.—Urinalysis showed the p_H of the urine to be 7.0, the specific gravity 1.014, with a trace of albumin and 4+ sugar. The urine was microscopically negative for blood. The blood sugar was 405 mg. per cent 5½ hours p.c., and the fasting level was 246 mg. per cent. The blood urea was 33 mg. The blood count revealed 4,990,000 R.B.C., 14,000 W.B.C., and 86 per cent hemoglobin. Wassermann and Kahn tests were negative. The basal metabolic rate was 36 per cent above normal. The urea clearance was 160 per cent the first hour, and the second hour, 160 per cent. A roentgenogram of the chest, November 8, 1937, was normal. *Clinical Diagnosis.*—Nodular goiter, with hyperthyroidism; essential hypertension; diabetes mellitus.

The patient was admitted to the hospital for preoperative preparation for thyroidectomy, during which time his diabetes was cared for, and a search made for the cause of the low-grade fever. Undulant fever agglutination was negative. A furuncle developed on the left forearm which required incision and drainage; others appeared later and when these disappeared, the temperature returned to normal.

A record of the blood pressure in the hospital is shown in Chart 4. It is interesting to observe that abnormally high readings were recorded on two occasions, the highest being 270/150. All readings, however, were at hypertensive levels.

The other significant observation made during his preoperative sojourn in the hospital was a pronounced polyuria. The urinary output varied from 9,000 to 16,800 cc. in 24 hours; this was attributed to an associated diabetes insipidus.

In view of the high basal metabolic rate, it appeared that the ideal treatment of the diabetes would include a relatively high calorie diet. His diet contained carbohydrates, 280 Gm.; protein, 86 Gm.; and fat, 100 Gm., supplying 2,364 calories daily. Amorphous insulin was given in four doses daily, the total daily dose varying between 50 and 150

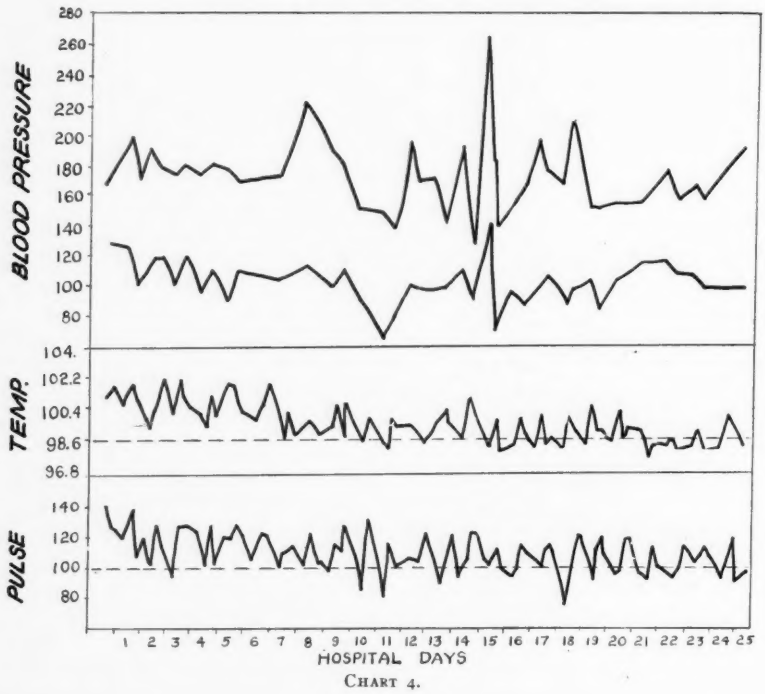

CHART 4.

units and was altered according to uranalysis done on four specimens daily and on blood sugar determinations done as often as three or four times daily. Chart 5 shows the extreme variation in blood sugar levels.

After 26 days in the hospital, his condition appeared not to have changed greatly, but he seemed to have reached maximum improvement and a subtotal thyroidectomy was performed. Although he had a rather sharp postoperative reaction this had subsided by the fourth postoperative day, and a normal convalescence was anticipated. However, on that day a furuncle appeared on the left cheek, which was quickly followed by cellulitis. In spite of all supportive measures the patient went rapidly downhill and died the following day.

Autopsy.—Only the pertinent findings at autopsy need be included for our purposes. Upon examining the abdomen the left kidney was in the normal position and of normal size. Occupying the right kidney region was a large, irregular, smooth, somewhat cystic mass the size of a grapefruit, which apparently involved the upper pole of the right kidney. The lower pole of the right kidney was easily felt and was considered to be of normal size and consistency. Lying on the aorta, just below the level of the renal

arteries, was a definitely encapsulated tumor nodule about 1.5 cm. in diameter which was similar in gross characteristics to the large tumor in the right suprarenal area.

Later dissection of the large mass showed it to be separable from the kidney and it was then recognized to be a large adrenal tumor (Fig. 2). The entire mass weighed 735 Gm. and was about 16 cm. in its greatest diameter. It was irregularly spherical and appeared to arise in the medulla of the right adrenal. On section, the tumor had a very large irregular central cavity, the lining of which consisted of a thick, shaggy, necrotic membrane. Surrounding this cavity was a mantle of tumor tissue varying from 2 to 3 cm. in thickness. In some areas the tumor appeared grossly to be very cellular, white in color, and to have relatively little stroma. In other areas the tissue was firmer, had a dusky, grayish-brown surface, and was traversed by considerable fibrous stroma. There

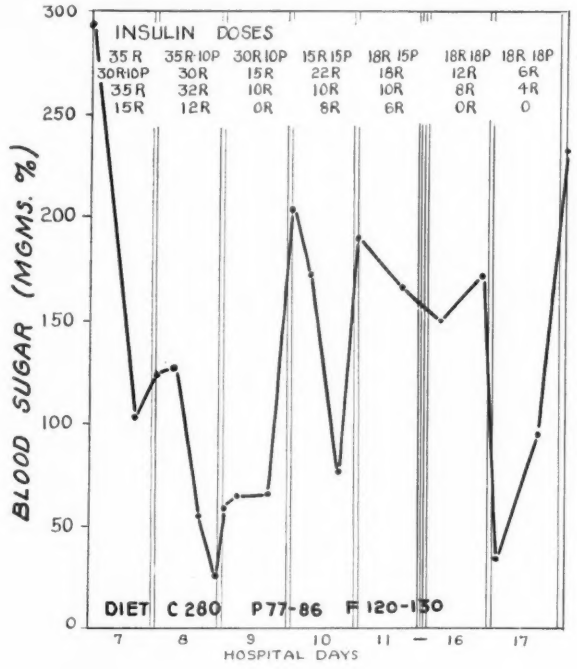

Chart 5.

was a fairly thick zone of quite dense sclerotic connective tissues separating the mantle of the tumor tissue from the shaggy lining of the central cavity.

The left adrenal weighed 15 Gm., which is about the normal weight of both adrenals. No tumor nodules were present.

Histologic Examination.—Sections from both adrenal glands showed large quantities of cortical tissue, the cells of which were quite large and stained less intensely and uniformly than usual. The cortical zones were not as well defined as usual. There appeared to be less than the usual amount of medullary tissue. Sections of the right adrenal showed an encapsulated tumor composed of cells of a single type but with extreme variations in size, shape and staining reaction. In general, they were comparable to the cells of the medulla rather than of the cortex. A section of the nodule removed from below the level of the renal vein showed the tumor cells to be of a type similar to those of the large tumor. *Pathologic Diagnosis.*—Pheochromocytoma of the right adrenal.

An associated finding of interest was the presence of cardiac hypertrophy, the heart weighing 450 Gm. The left ventricular wall averaged 2 to 2.5 cm. in thickness; the

right ventricular wall averaged 0.7 cm. There were moderately advanced atheromatous changes present in the aorta. The kidneys were grossly and microscopically normal and showed no active inflammatory process, and little or no sclerosis of blood vessels or glomeruli.

COMMENT.—The short duration of symptoms in this case is remarkable. Before operation it was observed that spikes of hypertension occurred but such elevations of blood pressure were thought to be associated with insulin reactions. In retrospect, it appears that we were unable to distinguish the symptoms due to frequent hypoglycemic episodes from a very similar set of symptoms which may have been associated with paroxysms of hypertension due to outpouring of large amounts of epinephrine; the patient's sympathetic nervous system being severely disturbed in both instances.

The blood sugar levels on the same food intake were extremely variable. It is not unusual for an individual with severe diabetes who is having his disease brought under control quickly to have insulin reactions, and, at first, in this case little attention was given to these. However, as days passed it was mentioned more than once at his bedside that it seemed remarkable for his blood sugar levels suddenly to fall to such low range without obvious explanation. Levels of 28 mg. per cent, for instance, were found. Later our attention was called to the fact that spells of nervousness, weakness and profuse perspiration occurred, which were considered at the time to be insulin reactions; yet blood sugar levels such as 98 mg. per cent, for example, were demonstrated at the height of symptoms. It was assumed that the extreme instability of the blood sugar levels was further exaggerated by hyperthyroidism and active infection. In the light of our present information the explanation would appear to be about as follows: First, it is probably correct to assume that the pressor substance released by such tumors is epinephrine (*vide infra*). When the amount of epinephrine poured out by the tumor was large, the glycogen was freed from the liver at a rapid rate, raising the blood sugar level. So long as this rate of epinephrine production was maintained, large amounts of insulin could be tolerated, but when it was withdrawn the blood was no longer flooded with sugar poured into it from the liver, and the insulin would cause a more rapid than normal deposition of glycogen in the liver, with tissue lack elsewhere and hypoglycemic shock. Whether diabetes actually existed might possibly be questioned, although in view of high fasting blood sugar levels and glycosuria, this seems acceptable. It is evident that the factors here are not present in the same relative proportions as are usually seen. There probably was some inherent weakness in the regulating mechanism for glucose metabolism, however, since other patients with high blood pressures from pheochromocytomata do not necessarily have anything comparable to clinical diabetes mellitus. Perhaps, if a more critical analysis of the oscillating blood sugar levels and of his "reactions" without hypoglycemia had been made, our attention might have been directed toward adrenal disease.

The question may be asked: Did this man have hyperthyroidism? If so, was it caused by or was it maintained by excessive quantities of epinephrine

in the blood? These questions cannot be completely answered. It is noteworthy, however, that he lacked such features of hyperthyroidism as exophthalmos, and presented others such as the extreme redness of the face and tongue as well as marked polyuria and high diastolic pressure not to be explained by thyroid disease. That the rate of blood flow through the tissues was excessive is consistent with his abnormally high urea clearance test, and this is a particularly interesting finding which points to the nonrenal origin of the hypertension. The rapid blood flow itself would be in keeping with the high metabolic rate and may also explain the severe polyuria. There are other points which seem to indicate that the hypermetabolism was of adrenal origin; namely, that his response to iodine was slight or questionable. The thyroid gland was not large; the portion removed at operation weighed 27 Gm. In considering this, it is worth noting that there was thrombosis and hemorrhage present which would increase the weight of the gland. There was a ruptured cyst, however, and some thyroid tissue was found at the lower left pole at autopsy. The pathologic report on the thyroid tissue removed was colloid goiter with a ruptured cyst. This does not offer any evidence that hyperthyroidism existed, and is quite consistent with the assumption that the hypermetabolism was of extrathyroid origin. His blood cholesterol was 125 mg. %, which is relatively low, and at a level frequently seen in hyperthyroidism, but this, too, loses its significance in view of the infection present as well as consideration of the relatively low level found in Case 1, in which the hypermetabolism disappeared on removal of the adrenal tumor.

One of the important features of this case was the presence of a secondary tumor lying on the aorta at the level of the renal arteries which had a gross and miscroscopic appearance identical with those of the large tumor. This probably represents a tumor of the organ of Zuckerkandl. This not only demonstrates the fact that such tumors are sometimes multiple and outside the suprarenal area, but also suggests an explanation for failure to obtain relief in some patients, by the removal of a single growth.

Embryology and Pathology.—The adrenal medulla has a common origin with the sympathetic nerve cells arising from the neural crest and is thus ectodermal in origin. It is part of the so-called chromaffin tissue, deriving this name from a brownish discoloration which it undergoes when fixed in a chromate solution. At birth it is represented, in addition to the adrenal medulla, by paraganglionic masses which usually degenerate as the adrenal medulla grows. Such masses may remain, however, and have been recognized chiefly in two locations. Kohn[5] called attention to a strip of chromaffin tissue situated ventral to the abdominal aorta and superior to the inferior mesenteric artery to which he gave the name paraganglion aorticum abdominale. Zuckerkandl[6] observed a pair of similar bodies in the region of the inferior mesenteric artery of the newborn, which have been known as the organs of Zuckerkandl. It is quite probable that these are the common sites of origin of aberrant pheochrome tumors, yet it is interesting to observe that in adrenalectomy experiments no hypertrophy or hyperplasia of these tissues

has been observed, which throws some doubt upon their functional capacity. Another chromaffin organ is the carotid body, but so far as we are able to determine, tumors of this organ have never produced sympathetic stimulation, nor have they been associated with hypertension.

Tumors of the adrenal medulla may be of three types: (1) Sympathoblastomata arising from immature sympathoblasts; (2) ganglioneuromata, from mature ganglion cells; and (3) pheochromocytomata, from mature chromaffin cells or pheochromoblasts. These have frequently been termed paragangliomata.

We are interested here only in the latter group which are well encapsulated, benign, nonmetastasizing tumors. They do not disturb their host by invasion, but by their functional activity are physiologically malignant. They vary greatly in size, having been observed varying from the size of a pea to that of a grapefruit. The size does not determine their activity. It is quite common for the larger ones to break down centrally, forming necrotic, cyst-like cavities.

They occur about equally in the sexes and although the autopsy cases reported earlier were more common in older people, clinical recognition has been much more frequent in young adults, the average age in the cases reviewed by Howard and Barker[7] being 27.5 years for the women, and 32 for the men.

There are certain features about these tumors which are of practical interest. For no known reason they are more prevalent on the right side. In the 103 cases reported by Brunschwig and Humphreys[1] there were 43 on the right and 34 on the left, while in the 20 surgical cases tabulated by McKenzie and MacEachern,[2] 15 were on the right and five on the left; a three to one ratio. In the cases collected by Howard and Barker,[7] this is even more outspoken; for of the 13 cases in which the tumor was situated in the adrenal gland, ten were on the right and only three on the left. As in our case, others have reported such tumors occurring away from the adrenal or in aberrant or heterotopic adrenals. Phillips[8] reports a case occurring in the apex of the left pleural cavity. He was able to find in the literature only 11 cases occurring outside the adrenal, and in nine of these the organ of Zuckerkandl was the site of origin, while one of the remaining two cases was in the right pleural cavity. The vast majority, however, will be found by a careful exploration of the renal area.

Microscopically, the tumor consists of nests or cords of polyhedral cells separated by thin connective tissue stroma, rich in capillaries. The cells vary in size and have large nuclei containing chromatin network. Mitoses are rare. Sections of the tumor fixed in bichromate solution show brown pigmented granules or diffuse brown pigmentation present in many, although not all, of the cells. This is evidence of secretory activity and is caused by some strong reducing substance, presumably epinephrine.[9] Epinephrine has been found to occur qualitatively in these tumors and quantitative determinations have been made, as in the case of Kelly, Piper, Wilder and Walters,[10] which

showed 120 mg. of crystalline epinephrine in half the tumor, and it was estimated that there would be 300 mg. in the entire tumor. All cases in which quantitative determinations have been made in these tumors have shown amounts of epinephrine far in excess of the amount normal for the adrenal medulla.

Diagnosis.—The diagnosis in these cases may be made by a careful analysis of the history. Paroxysmal attacks of hypertension have been recorded as the outstanding symptom in most cases, and this may be associated with precordial pain, tachycardia, pallor and flushing, and sensation of cold followed by heat; sweating, nausea and vomiting are not uncommon. Paroxysmal hypertension is not a prerequisite for the diagnosis, the hypertension being constant during the last period of observation in our first case. Persistent hypertension associated with pheochromocytomata has been mentioned previously by Wells,[11] and emphasized by Edward.[12] Vasomotor disturbances of some type which usually appear in definite seizures, apparently are present in all cases. Certain cases have simulated hyperthyroidism so closely as to lead to thyroidectomy. An elevated basal metabolic rate was present in both of our cases. This has also been reported by others.[2, 7] In seven of the cases in which the basal metabolic rate was recorded it was found to be distinctly elevated in three. In certain instances massage over the tumor may result in a sharp rise in the blood pressure.

We have been impressed with the unusually high renal function observed in our two cases. It appears that the secretion of these tumors stimulates the normal kidneys to increased function. In some cases diminished renal function may result from the disease. Also, as the result of the increased epinephrine, glycosuria and hyperglycemia are commonly observed.

There are several methods by which the roentgenogram may be of assistance in reaching a diagnosis. Often the plain film reveals a tumor shadow in the suprarenal area. Indirect evidence is also obtained by doing an intravenous urogram or a bilateral pyelogram, to see if there is any downward displacement of either kidney. Howard and Barker[7] stated that 11 of their 18 cases would have been demonstrated by making a pyelogram. A pyelogram in our second case would obviously have demonstrated the presence of a mass, but no change was observed by pyelography in our first case. In pyelography the size of the tumor is the important factor, and a tumor of considerable size is required to displace the kidney. Earlier methods of diagnosis of value before tumors reach such a size are desirable.

Visualization of these tumors by perirenal air injection has been employed by many, and its use in visualizing these tumors has been acknowledged by all. It is, however, not without risk, and fatalities have been reported from its use. Cahill[14] recently reported a large series of air injections, and feels that it is quite safe if certain fundamental precautions are observed. Joelson[15] has employed the procedure in a considerable number of cases without a serious event and feels that the secret of safety lies in the slowness of injection of the air. He takes 40 to 45 minutes to inject 300 to 400 cc., and in this manner

avoids all unpleasant sensations for the patient. We have done a small number of air injections and, although no fatalities have occurred, there have been two patients with reactions severe enough to cause hesitation in advising the procedure unless clear-cut indications are present. In cases in which a tumor is strongly suspected but cannot be demonstrated, we believe the surgeon should be prepared to undertake a bilateral exploration.

Treatment.—The treatment is surgical removal of the tumor, which can be expected to result in a cure, for this has been the result in all reported cases successfully operated upon, some now many years since operation. Even in the patients with persistent hypertension, removal of the tumor resulted in a prompt return of the blood pressure to normal.

The choice of operation depends upon a number of factors, not the least of which is individual preference. We have preferred the retroperitoneal operation after the technic described by Young,[4] which permits simultaneous bilateral exposure of the adrenals and avoids the increased risk of the transperitoneal approach. In cases in which the tumor is large, resection of the twelfth rib would greatly facilitate the operation.

The predilection of the tumors for the right side is worth remembering, but if there has been any doubt as to the side the tumor is on, this may be dispelled at the operating table, as in our case, even before the tumor is exposed. Manipulation of the area will produce a sharp rise in both the systolic and diastolic blood pressures, and when exposed, even the lightest pressure on the tumor is reflected in the blood pressure. The event, however, which requires careful preoperative planning is the clamping of the vessels and removal of the tumor. This is generally followed by a profound fall in blood pressure and possibly a state of shock. An ample supply of epinephrine must be ready, and in our case repeated doses were necessary in order to maintain the blood pressure. In addition to this, transfusion is almost essential, and this should be administered both during and after operation until the blood pressure is stabilized. We employed plasma transfusion during operation in our case, which served admirably to support the circulation.

Spinal anesthesia should be avoided because of its tendency to reduce the blood pressure. Basal anesthesia with avertin supported by light nitrous oxide and oxygen was satisfactory in our case.

No other method of treatment has been of any benefit. Deep roentgenotherapy has failed to bring any relief in the cases in which it has been tried. Nor is there any satisfactory palliative treatment for the attacks. Amyl nitrite has been suggested to relieve the hypertensive seizures in those patients presenting paroxysmal hypertension, but the nitrites otherwise have been of little benefit.

The recognition of the disease is most important, so that one may advise against any other operation, for these patients are poor operative risks and some of the deaths in such cases have followed other operations. Therefore, the only operation which should be performed is for the removal of the lesion which is producing the disease.

SUMMARY

Two cases of pheochromocytoma of the adrenal gland are presented.

In one case, severe diabetes mellitus existed, together with an extreme polyuria, amounting to as much as 16,800 cc. per day.

One of the cases was correctly diagnosed preoperatively with the help of clinical data and without the aid of demonstration of a tumor. In this case operative removal of the tumor has led to a complete cure.

It has been emphasized that paroxysms of hypertension are not a necessary part of the syndrome accompanying these tumors. The presence of hypermetabolism has been an outstanding feature in these cases. It is probable that hyperthyroidism was not present in either case and, in one, the hypermetabolism disappeared following removal of the tumor. Attention has been called to the diagnostic importance of high urea clearance.

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SACROCOCCYGEAL TERATOID TUMOR

CASE REPORT

GEORGE T. PACK, M.D., AND RALPH BRAUND, M.D.
NEW YORK, N. Y.
FROM THE MIXED TUMOR SERVICE, MEMORIAL HOSPITAL, NEW YORK, N. Y.

THE COMPLEX TERATOID TUMORS of spectacular appearance are rare neoplasms. They occasionally present difficult diagnostic and therapeutic problems. The sites of occurrence in the order of their frequency are the pelvis, the abdomen, the sacrococcygeal region, the thorax, and infrequently the nervous system. The teratomata of the newborn usually have a disorderly arrangement of germ layers, described by Ewing as a "pot-pourri" of fetal tissues. The presence of derivatives from all three germ layers, in contradistinction to the dermoid tumor, which is of ectodermal origin only, classifies these tumors as teratomata. Some teratomata may exhibit a more adult structure of their germ layers, even approaching the parasitic fetus, in whose development there is a more or less normal arrangement of organs. To this group, Ewing has applied the term "teratoid tumors."

A great variety of organs in various stages of development have been found, *e.g.,* from the ectoderm—nerves, epidermis and dermoid cysts; from the entoderm—bronchus, intestine, pancreas, liver and adrenal gland; and from the mesoderm—fibrous tissue, cartilage, bone, smooth and striated muscle. The sacrococcygeal teratoid tumors seem to be more prolific in producing rudimentary organs than those arising in other sites. The bone tissue may actually condense into well-formed extremities such as a forehand, hand, tibia, femur or toes. It requires no imagination to conceive of these complex sacrococcygeal tumors as the abortive half of a fused, monstrous, pygopagus twinning.

The teratoid tumor, with its great degree of tissue differentiation, seldom undergoes cancerous transformation. It has been asserted that the benignity of such a tumor can be assured, if muscle twitching, peristalsis or the presence of bone can be demonstrated. This statement is practically true, but there have been isolated examples of embryonal cancer developing in these tumors with local recurrences after removal and distant metastases causing death (De Veer, Browder, Renner, Goodsitt, Stewart and Craig).

Diagnosis.—In the group of published case reports, these tumors are more common in females than males—a ratio of more than 3 to 1. The presence of the tumor is usually observed at birth—65 of 72 cases, as reviewed by Chaffin. The tumor may be sufficiently bulky to complicate the delivery of the infant. If situated intrapelvically, the diagnosis may not be suspected until urinary or bowel destruction occurs.

The sacrococcygeal teratoid tumor must be differentiated from a pilonidal cyst, meningomyelocele, dermoid cyst and congenital anal atresia. A careful physical examination, and roentgenologic studies, usually lead to the correct

diagnosis. The meningomyelocele is compressible, and such pressure will cause bulging of the anterior fontanelle; furthermore, coughing and crying produce an expansile pulsation which is lacking in the teratoid tumor. The discovery of extraskeletal bone in the roentgenograms establishes the diagnosis of teratoid tumor. Although neurologic changes are not often associated with sacrococcygeal teratoid tumors, it should be borne in mind that defects of the spinal column, spinal cord and membranes may occur.

All sacrococcygeal teratoid tumors originate retrorectally, although they may arise dorsal or ventral to the sacrum. The teratomata situated on the dorsal aspect of the sacrum (see present case report) are rare in comparison with the same tumors springing from the anterior aspect or hollow of the sacrum. The origin is usually between the rectum and lower segments of the vertebral column; the tumor often grows downward to become extruded and hang as a sessile or pedunculated mass between the legs. If the tumor remains within the pelvis, obstruction to the urethra and rectum may occur.

Treatment.—Ewing has stated that one-third of the fetuses with sacrococcygeal teratoma are born dead and 90 per cent of the others die soon after birth. Those infants who survive should have their tumors removed as soon as their physical condition permits. The deformity itself sufficiently justifies the operation. Even though the tumor presents posteriorly, its growth may result in destruction, by pressure, of the gluteal muscles and fat. Pressure necrosis, ulceration and secondary infection in the tumor itself are serious complications of delay in treatment. The surgeon must use great judgment in deciding the optimal time for excision. The shock associated with this operation may be greater than expected. The intrapelvic teratoid tumors present a more difficult surgical problem. Inasmuch as these tumors are extraperitoneal and arise posterior to the rectum, the approach should never be through a suprapubic incision, but rather by resecting the coccyx and, if necessary, the terminal vertebrae (Pearse). In some instances the tumor can be shelled out without sacrificing any of the lower vertebral column, but the surgeon should never hesitate to do so to assure adequate exposure and complete removal.

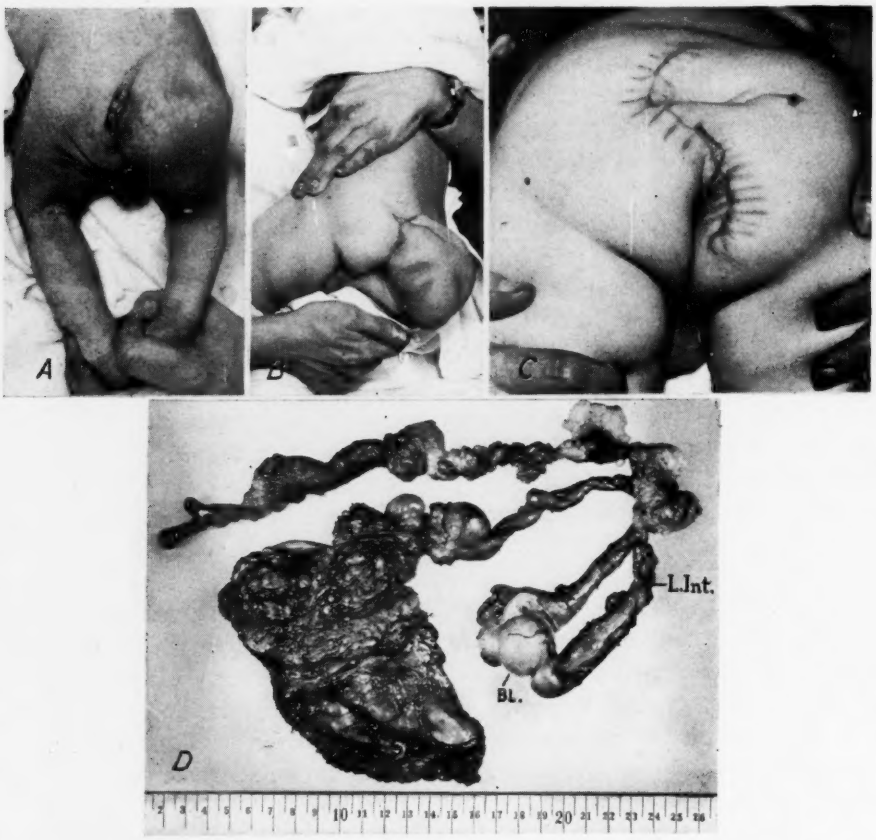
Case Report.—A. B., a male infant, four weeks old, was admitted to the Mixed Tumor Service of the Memorial Hospital, April 12, 1938. The delivery was reported as being normal, spontaneous and full-term. Since birth, the infant had been a feeding problem, and the third successive formula was being tried. A definite maternal and paternal history of twinning was obtained.

History.—At birth, a tumor mass was observed over the lower spine and right buttock. This increased in size in proportion to the child's growth. The mother stated that at birth there was a small but definite rudimentary umbilical cord attached to the mass. This later sloughed, leaving a small ulcer which remained unhealed. The mother also noted that when the child nursed there was a contraction over the lower portion of the mass. The tumor apparently caused the infant no pain and little inconvenience.

Physical Examination.—The child was a well-developed, slightly undernourished male infant, with a prominent tumor mass, measuring 8x7x4 cm., overlying the lower sacrum and right buttock. The tumor was covered by intact, elastic skin, except at one edge where there was a puckering of the skin which suggested a rudimentary umbilicus. The presence of this navel and antecedent cord indicated a high degree of tissue differen-

tiation, approaching a parasitic fetus in character. The consistency of the mass varied; in the upper portion were several small, round, fluctuant lobules; in the lower portion an irregular, firm nodule with definite skin attachment, resembling cartilage or bone. Stroking of the overlying skin produced two types of motility: (1) A superficial contraction of the skin, not unlike that seen in the cremasteric reflex; and (2) a deep vermicular movement similar to peristalsis within the contents of the mass. The child

PLATE I.



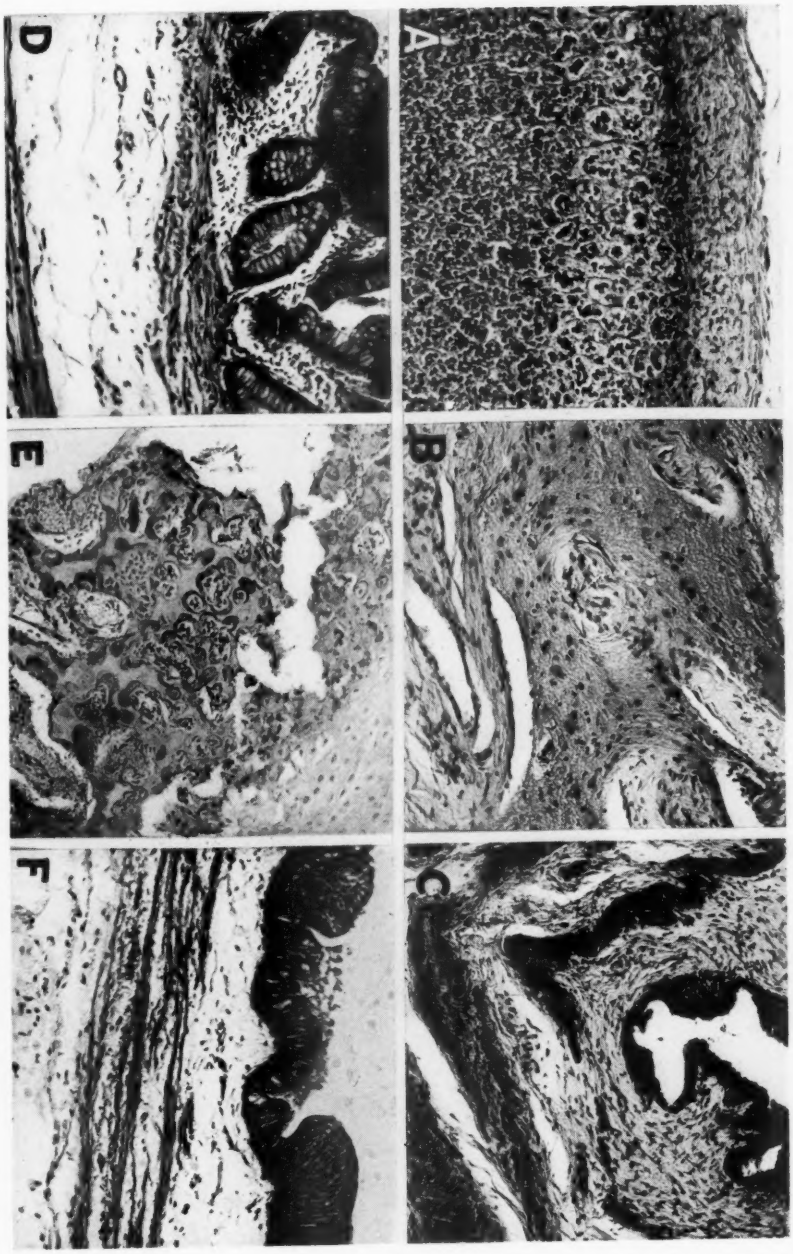
(A) Infant, age six weeks, sacrococcygeal teratoid tumor.
(B) Same infant, age 13 months. Preoperative condition.
(C) Postoperative condition.
(D) Gross specimen, showing 78 cm. of intestine; Bl. = urinary bladder; L. Int. = large intestine.

was permitted to nurse and, on swallowing, the same contractions took place as were produced by stroking. No sensory or motor changes could be demonstrated in the lower extremities. There was pronounced dilatation of the superficial abdominal veins. Roentgenologic studies showed no apparent defect in the sacrum and coccyx. Bony shadows of different densities were visualized roentgenographically within the tumor.

Treatment.—Surgical removal was not considered advisable until a later date because of the age, poor state of nutrition, and general physical condition of the child. Periodic examinations were made until the child was one year of age, at which time it was admitted for surgical excision of the tumor. During this year of observation, the increase in size of the tumor was not disproportionate to the growth of the child, as a whole.

Operation.—Performed under ether anesthesia, April 5, 1939: The tumor was excised

PLATE II.



(A) Well-formed adrenal gland. The medulla is lacking.
(B) Brain.
(C) Urinary bladder.
(D) Large intestine.
(E) Bone and cartilage.
(F) Bronchus.

through a wide elliptical incision. The dissection was relatively close to the capsule of the tumor and a good plane of cleavage was encountered except at the base where there was a stalk-like attachment to the sacrum. Adequate skin flaps permitted closure of the wound with interrupted silk sutures. A marginal stab wound was made for drainage. The postoperative course was uneventful, apart from a slight wound infection near the anus. The patient was discharged in good health on the seventeenth postoperative day. The child was seen recently (October, 1941) and showed no evidence of residual tumor. There was only a slight central depression of the scar over the sacrum.

Pathologic Examination.—The specimen consisted of an excised mass, surmounted by an ellipse of skin, measuring 8x10 cm. The subcutaneous tumor was made up of fat, connective tissue, bone, fragments of hair and a large length of intestine, which, when uncoiled, measured 78 cm. in length. It was divided into segments by occlusion of the lumen and contained a thick, greenish, mucoid substance which was chemically negative for the presence of bile. Along the course of this loop of intestine were situated three small out-pocketings, which contained clear, thick, mucoid material. A fourth globular out-pocket contained clear, watery fluid. *Microscopically,* this cloacal sac, or diverticulum, was identified as urinary bladder. Microscopic study of various parts of the tumor disclosed structures identifiable as well-formed adrenal (lacking medulla), poorly formed brain, fetal fat, epidermis, well-formed urinary bladder, large intestine, bone cartilage, and questionable bronchus.

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MALIGNANT DEGENERATION OF NEUROFIBROMATA OF PERIPHERAL NERVE TRUNKS (VON RECKLINGHAUSEN'S DISEASE)*

KELLOGG SPEED, M.D.
CHICAGO, ILL.

THE MALIGNANT DEGENERATION or metaplasia of neurofibromata of the large nerve trunks in von Recklinghausen's disease is the object of this report. Hosoi tabulated 65 cases in 1931, and since then several reports have appeared in the literature. The benign forms of the disease are often overlooked by the surgeon, but not by the dermatologist, whereas the dangers of incomplete operations or irritation of these tumors in peripheral nerves are almost unappreciated by surgeons, although pathologists, such as Ewing, have called attention to them.

Peripheral nerves composed of bundles of neuraxones running out from central nerve cells are bound together by various sheaths for the nerve trunk. Each neuraxone is surrounded by a sheath; the endoneurium is the connective tissue sheath outside the sheath of Schwann which encloses myelinated nerves. This endoneurium blends with the perineurium which binds bundles of smaller fibers together to form a fascicle, while the epineurium is a membrane enclosing the entire nerve trunk, composed of mixed collagenous and reticulin fibers. It is probable that peripheral neurogenous tumors, in most cases, develop from these sheaths. Some nerve trunks are even more complex, including sympathetic fibers and ganglion cells which may complicate tumor formation within them.

Ewing has classified the fibrous tumors arising from nerve trunks as:

(1) Cutaneous neurofibroma (fibroma molluscum, von Recklinghausen's disease).

(2) Neurofibroma of subcutaneous and deeper nerve trunks, divided into:

  (a) Plexiform neurofibroma.

  (b) Visceral neurofibroma.

  (c) Neurofibrosarcoma (neurogenic sarcoma).

von Recklinghausen's neurofibromatosis has protean manifestations. Many of its tumors have no apparent relation to nerve tissue as such, but may simulate multiple forms of lipoma, myxoma, pure fibroma and the multiple foci of sebaceous gland hypertrophy seen in Pringle's disease. Multiple forms of keloid fibroma may be confused with and included in the concept of neurofibromatosis.

Garré, in 1892, described primary sarcoma of nerves not associated with von Recklinghausen's disease, and secondary sarcoma of nerves due to sar-

* Read before the Central Surgical Association, Chicago, February 27, 1942.

comatous degeneration of preexisting neurofibromata, a part of von Recklinghausen's disease. Primary sarcoma of nerves is usually very malignant, with rapid growth and invasion of surrounding tissue, leading to internal metastases without local or regional recurrence. In the secondary form, developing in peripheral nerves of patients, subjects of von Recklinghausen's disease, the sarcoma develops in one of the preexisting neurofibromata, possibly following trauma or for no known reason, and begins to enlarge quite rapidly. It is at first enclosed in its fibrous capsule where it may remain for a long time. It early becomes painful and later causes excruciating distress in its invasion of large sensory nerve trunks. If operation is undertaken, usually resulting in incomplete removal of the growth, recurrence follows rapidly, with great pain, local growth and distant metastases much delayed. The occurrence of sarcoma in the neurofibroma of peripheral nerves averages from 8 per cent to 15 per cent according to various authors. Other tumors of von Recklinghausen's disease, not necessarily situated in large nerve trunks, seem to be incited to rapid growth and possible malignant degeneration by such operative interference. It is because of the failure of the surgeon to recognize these points that these two case reports, out of 15 instances of neurofibromatosis (von Recklinghausen's disease) admitted to the Presbyterian Hospital, Chicago, appear worthy of record on account of sarcomatous degeneration of large peripheral nerve trunks.

CASE REPORTS

Case 1.—R. F., female, married, age 35, was admitted March 10, 1915, finally discharged March 17, 1916. Death in January, 1917, from metastases in the lungs and brain.

She had carried the manifestations of von Recklinghausen's disease, with many tumors, and café-au-lait spots, since childhood. Her complaint was a swelling of the left thigh behind the knee, which had begun in June, 1915, causing at first dull and later shooting knife-like pains in the sciatic distribution. She was emaciated. There was a history of a fall on the ice 12 years before, followed by development of this tumor and one near the head of the left peroneous longus origin. Her mother, and all of her seven children, had multiple pigmented moles; one brother and one sister had multiple subcutaneous tumors similar to the patient's. The mass of her left thigh measured 47.5 cm. in circumference, compared to 25.5 cm. for the right thigh. The left leg was normal except for some edema and interfered with function on account of the size of the tumor. Operation to disarticulate the hip was performed March 16, 1915, by Doctor Phemister. A diagnosis of sarcomatous degeneration of neurofibromata (von Recklinghausen) was made. The histology showed many forms of cells varying from small round to spindle in character along with mitotic figures. No nerve tissue was distinguished.

Case 2.—O. P., male, age 23, married, was admitted on several occasions between September 16, 1937 and October 2, 1941. This man was studied over four years, as a sufferer from neurofibromatosis, with quite large tumors developing in several peripheral nerves—sciatic, radial and median. The tumor in the right median nerve finally led to amputation of the right arm high up, following a diagnosis of sarcomatous degeneration. He is still alive, February, 1942, with no evidence of metastasis.

Since childhood he had had multiple soft tumors of the skin in various parts of the body, along with multiple spots of brownish pigmentation. The tumors were not painful and they now feel like fatty, discrete protrusions, all sessile and not pedunculated. In 1933, he developed a mass in the right thigh, posterior aspect, which has increased in volume until it has reached the size of a grapefruit. This interfered with sitting and full extension of the leg, and was accompanied by pain in the sciatic distribution. Shortly

after the tumor of the sciatic nerve developed, in 1933, there appeared in the right forearm, on the volar aspect, a similar mass which at first was not painful but led to weakness in the hand, although some motions of the hand and fingers were still possible. The principal interference was confined to median nerve distribution.

The thigh tumor seemed so hard in one area that calcification was suspected, although the tumor seemed to infiltrate into the muscle spaces like a diffuse lipoma. It was evidently part of the von Recklinghausen's disease present.

FIG. 1.—Case 2: Back view in 1937, when a small lumbar tumor was removed for histologic examination. The discolored (café-au-lait) spots and innumerable tumors are seen.

The blood was normal and the Wassermann test was negative. The forearm tumor had begun to become painful for the last five weeks and, in the last four months, had assumed rapid growth. The subjective sensation in the forearm was one of throbbing, accompanied by prickling up and down the arm and constriction near the center of this mass. Some of this distress was relieved temporarily by aspirin and by extending his arm above his head.

On September 18, 1937, one of the small tumors in his lumbar region was removed for histologic study. This had nonmalignant fibrous characteristics. Two days later, the large tumor of the right thigh and sciatic nerve was removed and showed no malignant findings, nor did there develop any recurrence in the next four years.

On September 28, 1937, a nine-inch incision was made on the volar aspect of the

right forearm. A large whitish mass was uncovered just beneath the bellies of the palmaris longus and the flexor carpi ulnaris, which had been split to expose the field. The tumor was almost cartilaginous in consistency and appearance and was intimately associated with the sheath of the median nerve. Several smaller tumors, more fibrous in character and round in shape, lay in proximity to the main mass. All were dissected away without known injury to the median nerve, though some spots in the sheath of the nerve had to be cut away by the sharp dissection. The nerve was dropped back into place, muscle and fascia were closed over and the skin sutured.

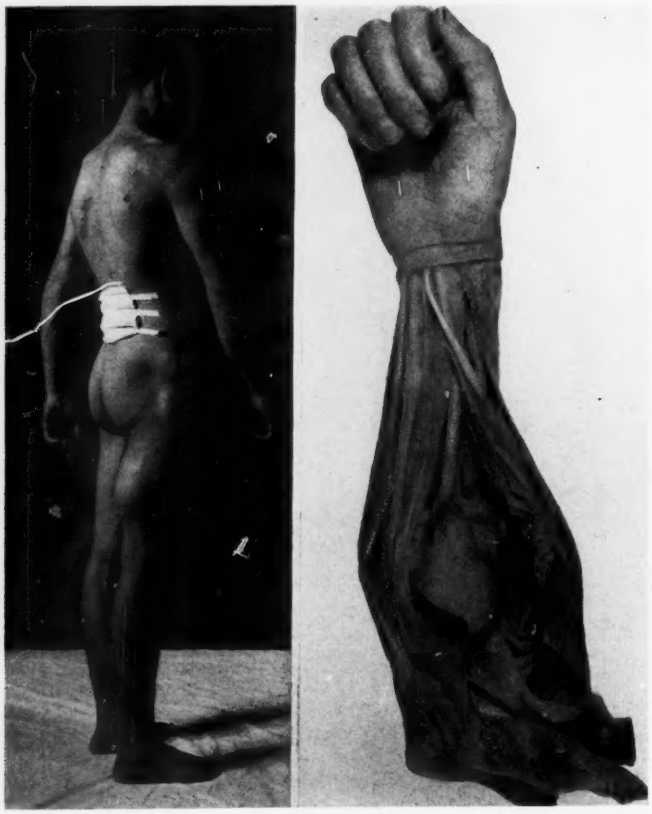

FIG. 2. FIG. 3.

FIG. 2.—Case 2: Showing tumor of sciatic nerve before removal in 1937. No recurrence to date.

FIG. 3.—Case 2: Forearm specimen (1941) after amputation showing final recurrence after two operations of tumor of median nerve. It is still fairly well encapsulated but the nerve is grossly enlarged in both directions.

On section of this mass, no ulceration or destruction of tissue was seen, only loose fibrillar structure in which were embedded spindle- and stellate-shaped nuclei. Most of the fibrils were indistinct with amorphous spaces between them. There were some collections of lymphocytes. No tissue identifiable as nerve fiber could be found.

On August 24, 1940, this tumor had recurred locally, with increased pain, and a second removal was attempted by a similar procedure. At this time, the tissue appeared more collagenous and myxomatous and spread out, invading surrounding tissue and the nerve sheath, extending almost to the elbow, so that complete surgical removal was not possible. A section showed rare mitotic figures. After this wound healed, he was given about 1,000 r. roentgenotherapy.

On June 10, 1941, on account of the severe pain, the median nerve just below the elbow was injected first with a small amount of novocain and then with several cubic centimeters of absolute alcohol. At this time, there had now appeared a rapidly growing tumor, nearly the size of a small orange, on the radial nerve at the back of the arm. This was exposed and the mass, 3×1.5 inches, was surgically removed. Its invasion of the nerve was such that the main trunk was severed and, although a few fibrils were preserved, the nerve was mostly destroyed and a drop-wrist followed. A cock-up splint was applied, and for a while the pain disappeared.

Both pain and local recurrence followed rapidly. The tumor again appeared larger in the forearm than it had ever been, and after a clinical diagnosis of sarcoma, amputation of the right arm was proposed and performed, October 3, 1941. The level of the amputation was well above the site of the incision for removal of the tumor on the radial nerve. In the arm tissues it was seen that the middle trunk of the brachial plexus was grossly enlarged and thickened to about three times its normal diameter, as if the tumor mass had invaded this trunk and was extending upward. The cut off trunks of the plexus were injected with absolute alcohol. There had been no local recurrence or metastases yet.

CONCLUSIONS

Development of pain in the distribution of a peripheral nerve, the site of a tumor in a patient afflicted with von Recklinghausen's disease, is highly significant of sarcomatous degeneration of that tumor.

Excision of any tumor mass involving a peripheral nerve in this disease must be cautiously undertaken and thoroughly performed. It may lead to local recurrence and distant metastases or excitation of other tumors of the disease elsewhere in the body.

When sarcomatous change is suspected, early amputation, if possible, is probably the treatment of choice. In the reported cases in the literature, roentgenotherapy in its present state at least seems unavailing.

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CANCER OF THE CERVICAL ESOPHAGUS

WILLIAM L. WATSON, M.D.

NEW YORK, N. Y.

FROM THE THORACIC SURGICAL SERVICE, MEMORIAL HOSPITAL, NEW YORK, N. Y.

THE ULTIMATE AIM of the surgeon in dealing with diseases of the cervical esophagus has been to devise a safe and adequate operation for the cure of cancer in this locality. A brief review of the history of surgical progress in this field seems indicated, and, although many notable names are identified with this work, it is possible to mention only a few of the major contributions in this report.

The earliest and simplest recorded esophageal operation was an emergency esophagotomy for the extraction of a foreign body carried out by Goursauld,[8] in 1738. Some 80 years later, it was first successfully performed by Roland.[12] Later, in 1833, Arnott[1] attempted the operation at the Middlesex Hospital, but the patient died 56 hours after operation. In 1858, Cock[4] had a successful venture, and, in 1868, Cheever[3] reported two successful cases. It is of interest to note a lack of reports in the literature dealing with the surgical extirpation of the cervical esophagus until 1871, when Billroth[2] reported on his surgical experience with the dogs' esophagus. The paucity of subsequent medical reports dealing with the esophagus in general and the cervical portion in particular leads to the suspicion that a scarcity of suitable operative material, coupled with a shockingly high operative mortality, tended to discourage surgical endeavor along this line.

The cervical esophagus was not considered a suitable province for surgical endeavor until 1877, when the first human cervical esophagus was extirpated by Czerny.[5] He made an incision along the left anterior border of the sternocleidomastoid muscle, mobilized and excised a segment of cervical esophagus, six centimeters in length, sutured the distal opening into the lower angle of the wound and used it for feeding purposes. His patient made a satisfactory postoperative recovery, but died of recurrent cancer 15 months later. This pioneer operation opened the cervical esophagus to surgical attack.

The second surgical advance in this work was by Mikulicz.[10] In 1884, he resected a cervical esophagus for cancer and performed a plastic-flap repair of the postoperative fistula, which was technically successful and permitted his patient to enjoy eating solid food ten days after operation. Recurrent cancer caused the death of this patient 16 months later.

Von Hacker,[15] in 1908, reported a review of the literature, including a collected series of 25 cases, with an operative mortality of 48 per cent. The longest survival in this group was 16 months. He added a case of his own in which a gastrostomy was followed by a resection of the cervical esophagus and complete extirpation of the larynx. Later, a two-stage plastic procedure was

successful in fashioning a skin tube of two lateral rectangular skin flaps. His patient was living and well 16 months after operation, and had gained 40 pounds in weight, but the final result is not recorded.

Lane,[9] in 1911, reported that he had resected a cervical esophagus and had

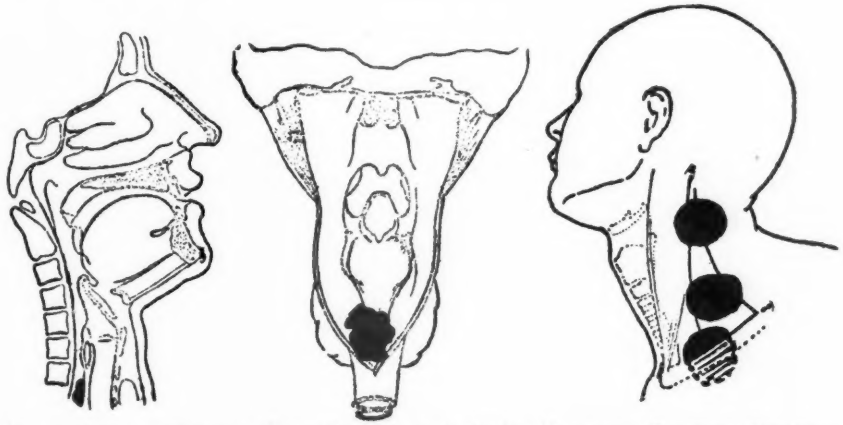


FIG. 1.—Case 1: *Carcinoma of Upper Esophagus with Cervical Metastases. Treatment:* Roentgenotherapy: 5 cm. port., ant. neck, 2500 r. Gold-filtered radon seeds: Neck nodes—total 103 mc.

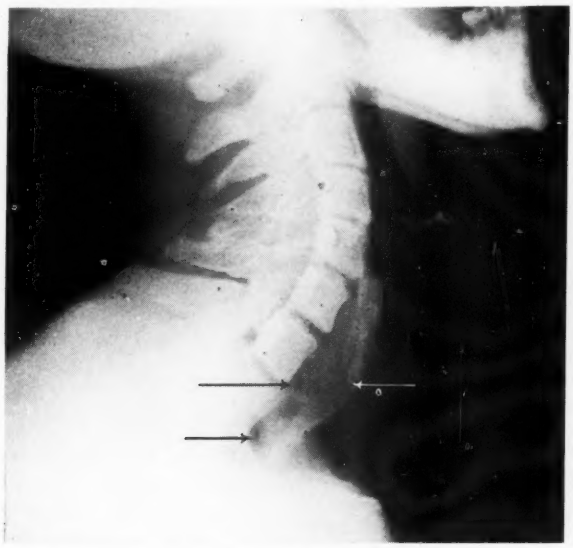


FIG. 2.—Case 1: Roentgenogram showing the tumor of the first portion of the cervical esophagus.

used a single horizontal skin flap with its base in the left neck to close the defect, suturing it to the upper and lower edges of pharyngo-esophageal defect. After firm continuity of the tube was established, recurrent cancer invaded the carotid artery and caused a fatal hemorrhage.

Eggers,[6] in 1925, reported a case of resection of the cervical esophagus and larynx for cancer, and the following year (1926) Torek[13] reported a similar

case. Unfortunately, both these patients died of their disease shortly after operation.

Sir Wilfred Trotter,[14] in 1937, reported a ten-year surgical cure. His patient came to autopsy and no evidence of cancer was found. A considerable amount of hair had grown into the lumen of the reconstructed cervical esophagus.

Arthur Evans,[7] another English surgeon, reported a 23-year cure of cancer of the cervical esophagus by radical excision of the cervical esophagus and larynx.

Case 1 reports the successful management by a combination of radiation and surgical measures of a patient with cancer of the cervical esophagus presenting three separate cervical lymph node metastases. This patient is alive and in good health five and one-half years later.

Case 1.—*Carcinoma of Cervical Esophagus:* G. M., male, age 70, was admitted to Memorial Hospital, April 1, 1936. For a year he had noted the gradual enlargement of a lump in his neck accompanied by increasing nervousness and slight difficulty in swallowing. Examination revealed an elderly patient of the thin, wiry, highly nervous type. In his left neck, there were three masses. The largest one was four centimeters in diameter located beneath the sternocleidomastoid muscle and apparently attached to the left lobe of thyroid gland. A smaller mass was noted at a higher level, and the third was partially palpable behind the left sternoclavicular junction (Fig. 1).

A node was removed and reported as showing metastatic epidermoid carcinoma, and the working diagnosis of carcinoma of the thyroid had to be dropped. Radiographic studies suggested a lesion of the upper cervical esophagus (Fig. 2), and direct examination revealed a small outcropping of cancer at the esophageal entrance. A biopsy was obtained to confirm the diagnosis.

The neck masses were surgically exposed and gold-filtered radon seeds with a value of 88 millicuries were inserted. At a later date a dose of 15 millicuries was added, making a total of 103 millicuries. Roentgenotherapy was instituted and 2,500 r. was administered through a five-centimeter lower neck portal.

It is now five and one-half years since treatment was started. The patient has gained a little weight, and has no eating difficulties except those he attributes to the lack of a lower dental plate. The treated side of his neck is atrophic and fibrotic, with telangiectasis of the overlying skin, and there is a suggestion of a left Horner's syndrome.

Five other patients were explored who had cancer of the cervical esophagus and inoperable extensions of the disease found; in each instance gold-filtered radon seeds were inserted at operation, without, however, influencing the rapidly fatal termination of the disease.

Jens Nielson,[11] of the Radiumhemmet, reported, in 1940, the history of a 48-year-old housewife with cancer of the cervical esophagus free of disease six and one-half years after aggressive radiation therapy. The patient was symptom free in 1940, and had gained six kilograms in weight.

Case 2.—*Carcinoma of Cervical Esophagus:* J. F., male, age 69, was admitted to Memorial Hospital, July 21, 1937. For three months he had noted gradually increasing dysphagia accompanied by a feeling of substernal pressure and a sore throat.

On examination, the patient had the pasty, emaciated appearance, typical of his disease. Esophagoscopy revealed a bulky, friable, cauliflower-like mass in the first portion of the cervical esophagus. A biopsy study was reported as epidermoid carcinoma,

Grade 2. Roentgenograms revealed a filling defect in the upper esophagus and a soft mass causing partial obstruction of both food and air passageways (Fig. 3A and B).

Treatment was by divided doses of roentgen ray, and his reaction was quite severe. The initial edema caused a dangerous narrowing of the trachea and a tracheotomy was necessary. Later, regression of tumor was complete, and the tube was soon discarded. A gain of 17 pounds in weight was noted, and periodic bougie dilatations have maintained a relative freedom from dysphagia for a period of more than four years. Myocardial fibrosis and coronary artery disease complicate this man's prognosis.

(A) (B)

FIG. 3.—Case 2: Roentgenograms showing (A) the large tumor of the cervical esophagus causing marked tracheal compression and (B) postradiation regression. The patient is alive and well over four years.

It is agreed by most observers that cancer of the cervical esophagus causes one in every 100 deaths due to neoplastic disease. In other words, the disease is a relatively common one, and the material for its study should, therefore, be adequate. Hoarseness, pain and dysphagia are the usual symptoms, and they occur quite early in the course of the disease. The cervical esophagus is well known to be surgically accessible. Given a common disease, located in a readily accessible portion of the body, and calling attention to itself by early symptoms, one may then ask why "cancer of the cervical esophagus is still the realm of experimental surgery."

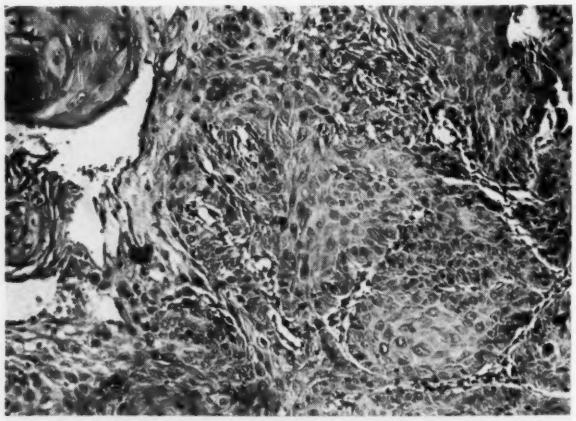
For a number of years, I have been interested in cancer of the esophagus and have reviewed much of the older literature and most of the recent reports dealing with this disease, and it is obvious that there has been a considerable revival of interest in the surgical approach to the problem of cancer of the esophagus. The improved anesthesias now available, the efficient chemicals at hand to combat infection, and an improved surgical knowledge of the parts involved encourage one to take an optimistic position as regards the future control of this disease.

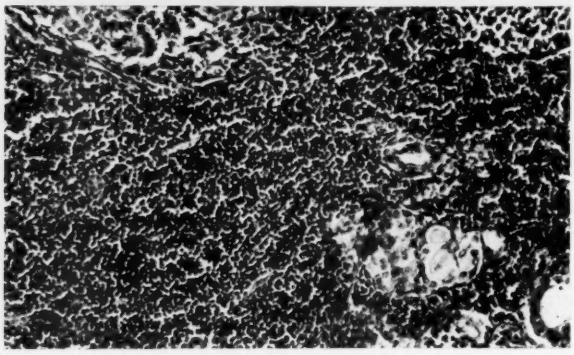
At the same time, it must be remembered that adequate cancer surgery requires not only that the patient make a satisfactory postoperative recovery, but he must also live long enough to warrant the conclusion that his neoplasm has been completely removed. A technically successful operation for the ex-

tirpation of a cancer does not, in itself, entitle the operator to the privilege of reporting his experience.

In one recent case of cancer of the cervical esophagus treated by surgical extirpation and plastic repair, the method of attack was suggested by the report of a ten-year cure by Mr. Wilfred Trotter.[14] The exact sequence of

(A)





(B)

FIG. 4.—Case 3. (A) Cancer of the cervical esophagus. (B) Hashimoto's struma.

events in our patient's surgical career does not appear in the medical literature of the past, and so may afford a practical basis for future effort and also serve to point out certain pitfalls to be avoided.

Case 3.—*Carcinoma of Cervical Esophagus:* S. I., female, age 49, had complained of dysphagia for seven years, with occasional episodes of complete obstruction caused by a bolus of food which could be dislodged only by induced vomiting or by swallowing water. A diagnosis of carcinoma of the first portion of the esophagus was established in March, 1940 by Dr. Wm. Wuester, who discovered a small lesion on esophagoscopy and took a biopsy (Fig. 4A). A Janeway-type gastrostomy was performed by him, and the patient was then referred to the Thoracic Surgical Service at Memorial Hospital.

Treatment has been by surgical measures, and a number of steps have been necessary. The first procedure was carried out under intratracheal cyclopropane anesthesia.

A wide rectangular incision was made across the lower neck, with its base on the left side. The lower half of the right sternocleidomastoid muscle was excised, revealing a hard, adherent, right lobe of thyroid gland, which was also removed (Fig. 5). (Histologically, this proved to be a Hashimoto's struma (Fig. 4B) and not cancer infiltration.) The esophagus was mobilized and the prepared skin flap placed behind it and the wound closed (Fig. 6). During the subsequent ten days, tension and interference with blood

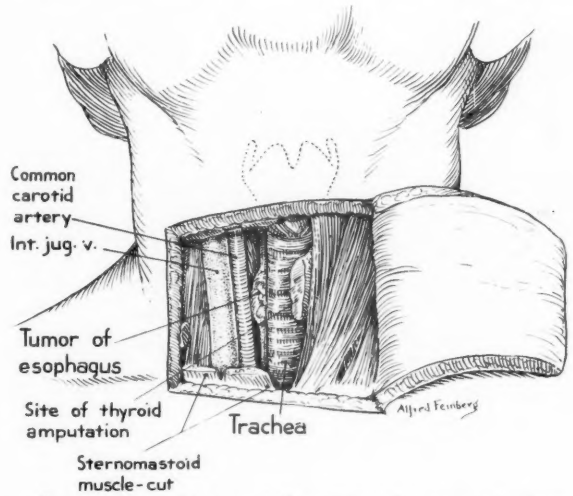


FIG. 5.—The right sternocleidomastoid and strap muscles have been excised and the right lobe of the thyroid gland removed exposing the cervical esophagus and the tumor.

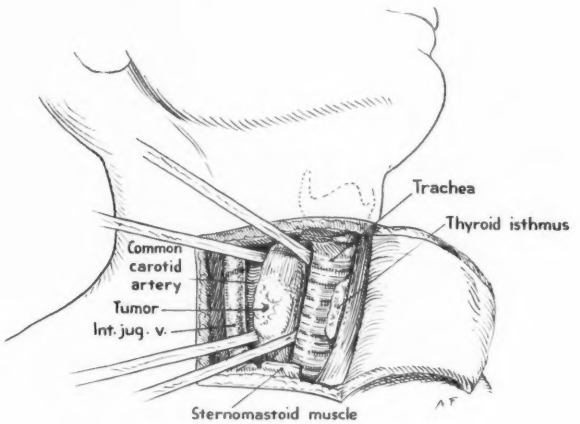


FIG. 6.—The esophagus has been mobilized and tapes passed around it, above and below the tumor.

supply caused necrosis of the exteriorized portion of esophagus, and at the second operation the necrotic portion was removed by cautery and the upper and lower apertures sutured to the skin (Fig. 7).

During the next eight months various unsatisfactory measures were employed in an attempt to maintain a communication between pharynx and esophagus. When the stricture finally closed and obstruction became complete, the first step in the plastic reconstruction was carried out under local anesthesia by opening the right side of neck, excis-

ing old scar, mobilizing trachea and larynx and placing in the defect a large Padgett skin graft. This graft was obtained from a comparatively hairless portion of the right lower abdomen, and it healed in place by primary union (Fig. 8).

After an interval of three months, the patient was readmitted and a retrograde esophagoscopy was undertaken and a small olive-tipped bougie was passed upward to

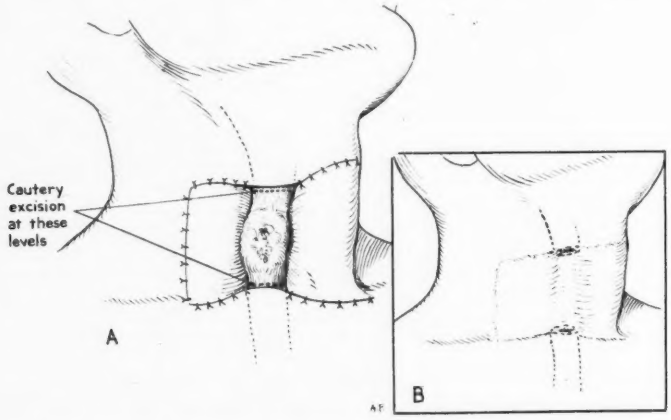


FIG. 7.—(A) The tumor has been exteriorized by passing the trapdoor-flap of skin and platysma beneath the esophagus and closing the incision about it. (B) Ten days later the tumor was excised with the actual cautery.

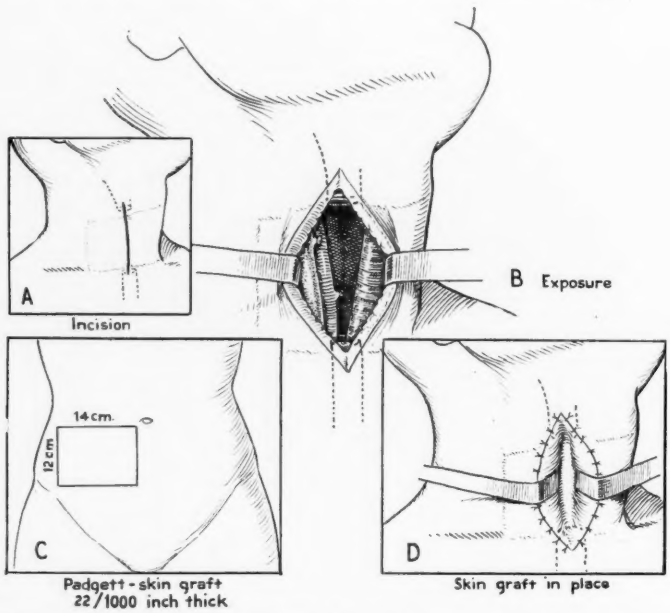


FIG. 8.—Plastic repair: (A) and (B) show the incision and the exposure. (C) The hairless site of skin graft. (D) The graft in place.

the point of obstruction in the lower neck. A small incision was made in the graft at the point where the bougie could be palpated (Fig. 9). A black silk thread was then tied to the bougie and brought out through the gastrostomy stoma. The optimum point for incising into the pharynx was located in the same fashion (Fig. 9), and the same black silk thread was then brought out the patient's mouth and anchored to the skin of the cheek (Fig. 10).

After a short interval, the apertures were greatly enlarged and an accurate approximation of skin and mucous membrane was obtained.

The final operative step was carried out June 3, 1941. The anterior wall of esophagus was formed by infolding the lateral portions of the graft so as to form a continuous tube from pharynx to esophagus (Fig. 11). Five grams of sulfathiazole was then placed in the

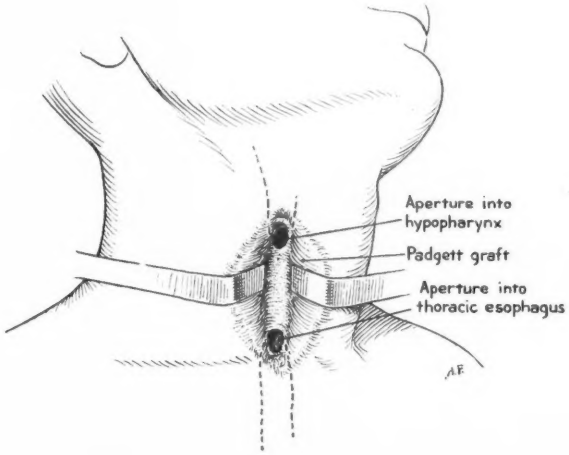


FIG. 9.—Showing the new apertures into the pharynx and proximal esophagus.

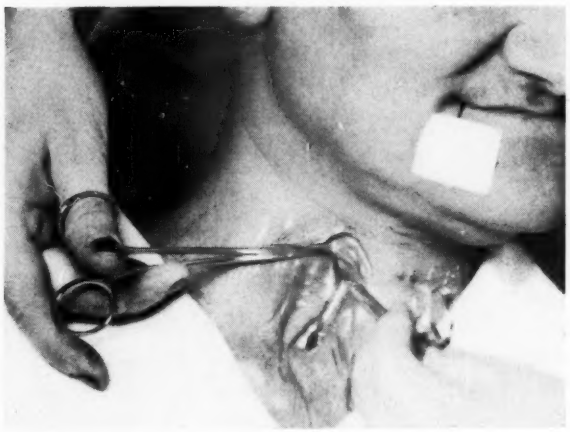


FIG. 10.—Case 3: Apertures have been made in the upper and lower angles, and a string passed from the mouth down to, and through the gastrostomy stoma.

wound, and the skin edges closed without tension over the tube. A full liquid diet was taken on the seventeenth day postoperative, and soon the patient was allowed a normal diet (Figs. 12 and 13).

Comment.—This patient had a very early cancer of the cervical esophagus developing in an area of leukoplakia, probably the result of chronic partial obstruction of thyroid origin. She is well only 18 months after excision of

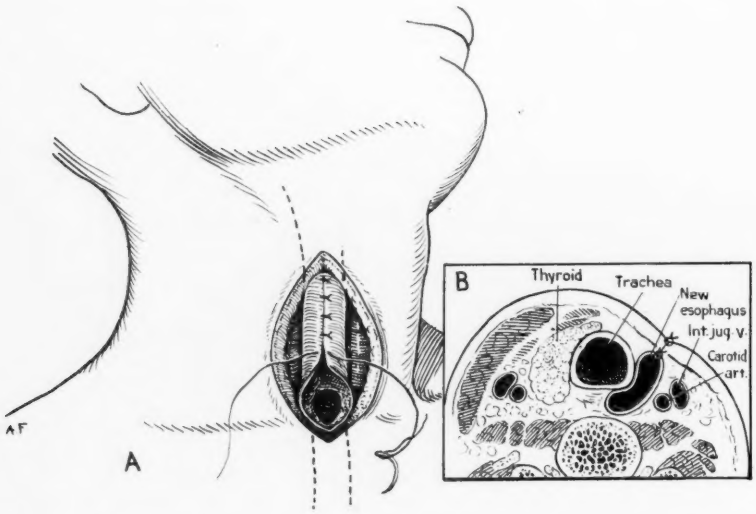


FIG. 11.—Showing the formation of a new skin graft-lined tube connecting the pharynx and the esophagus.

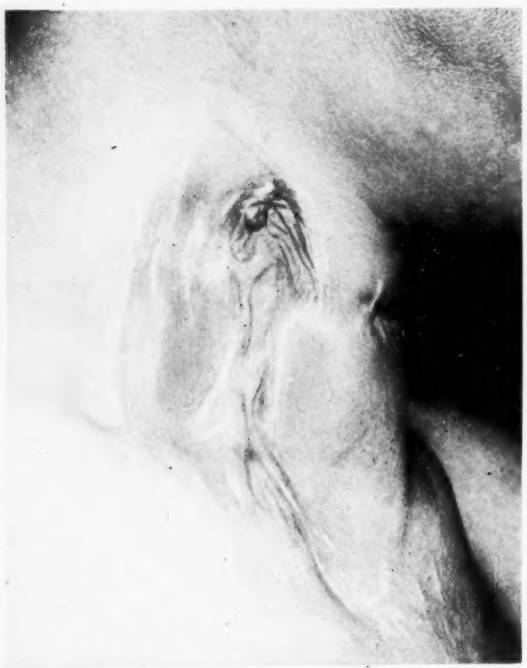


FIG. 12.—Photograph showing the patient after the final stage of the plastic closure.

the esophagus, and time alone will determine whether or not she is cured of her cancer. One can only hope that stricture or rupture will not occur or an overgrowth of hair cause esophageal obstruction.

One patient with cancer of the cervical and upper thoracic portions of the esophagus was treated by gastrostomy and transthoracic and cervical esophagectomy in June, 1941. The patient made a surgical recovery, but it is too

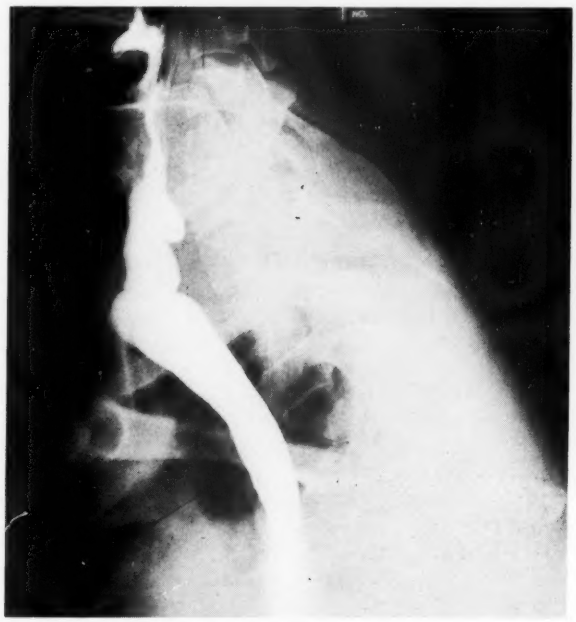


FIG. 13.—Case 3: Roentgenogram showing the reconstructed cervical esophagus after barium swallowing.

recent a case to warrant discussion as to the value of this procedure. However, it is safe to say that this approach allows the operator an opportunity of accomplishing a fairly wide tumor excision, and may do much to prevent the high recurrence rate noted in the literature.

SUMMARY

Cancer of the upper esophagus is shown to be a "curable" disease by radiation measures. A surgical approach to the disease, with a method of tubular reconstruction, is described in a detailed case report.

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(Note.—The discussions contain references to benign conditions of the cervical esophagus which formed a part of the original report as presented to the New York Surgical Society. These benign conditions have not been included in the paper for publication.)

DISCUSSION: DR. JOHN H. GARLOCK (New York) said that there is a rather general agreement today concerning the surgical treatment of a pulsion diverticulum of the cervical esophagus. The only point for discussion is concerned with a one- or two-stage operation. Doctor Garlock believes that, in average hands, the two-stage procedure is a safer one and probably is most often utilized throughout the country.

With respect to cancer of the cervical esophagus; it has been the experience of most observers that the majority of these cases report for treatment after the tumor has become inoperable. Most of the patients that he had seen had been treated by radiation methods. The unusual result reported by Doctor Watson, in a male, age 70, can be attributed, in great part, to the low-grade malignancy of these tumors usually seen in the aged, and to the rapid response to radiation therapy. Most of these cases reported in the surgical literature have not survived more than one year.

With respect to the surgical treatment of carcinoma of the cervical esophagus, numerous methods have been devised, the most radical of which is that described by Eggers. In his operation, the larynx as well as the cervical esophagus is excised, and a permanent tracheotomy is made in the suprasternal notch. In early cases Doctor Garlock said he could visualize a radical resection without removal of the larynx, and Doctor Watson has demonstrated that this can be done. The idea occurred to Doctor Garlock, as Doctor Watson was describing the operation, that, at the time of the original mobilization of the organ, instead of fashioning a flap of skin and placing it beneath the exposed esophagus, thereby placing the esophagus under greater tension and jeopardizing its blood supply, it might be feasible to place a free split-thickness skin graft beneath the esophagus, epithelial surface forward, in order to form a skin-lined base for future aid in reconstruction. The pressure of the mobilized esophagus on the graft would facilitate complete "take" of the transplant. This maneuver would save many steps in the subsequent reconstructive process.

DR. HOWARD LILIENTHAL (New York) said that in all his years of operating he could remember but a single case in which he dealt surgically with a pulsion diverticulum in the neck. In that case the opening into the esophagus was larger in diameter than that of the esophagus itself. When the diverticulum was full, the overflow entered the esophagus. The patient, a male, age 55, had been ill a long time, and was emaciated and weak. No gastrostomy was performed, but the procedure employed was one devised by another surgeon (Doctor Lilienthal thought by the late Doctor Freeman, of Denver). Through an incision in the left side of the neck the diverticulum was withdrawn and anchored with a ligature to the ear, so that the opening into the gullet was its lowest part and the sac was kept empty by gravity. There was immediate improvement and, in about three weeks, the second stage was performed. This consisted in the ablation of the sac and suture of the wound in the esophagus. The convalescence was stormy, and for a short time there was some slight leakage through the skin wound. Eventual and complete recovery followed, and Doctor Lilienthal had seen the man at intervals for a number of years. The case was reported before the New York Society for Thoracic Surgery, and published in the Journal of Thoracic Surgery, St. Louis, vol. 5, No. 5.

In regard to long-continued treatment by radiation, Doctor Lilienthal asked Doctor Watson if there might not be danger of epidermal malignancy. A number of years ago Doctor Lilienthal saw a patient who had been treated with radiation for goiter and there developed a quadrangular epithelioma; its area was that of the shield which had been used to confine the space treated by the rays. The patient was shown before the American Surgical Association.

DR. WILLIAM L. WATSON (closing) said that Doctor Garlock's suggestion that a primary skin graft could possibly have been carried out at the original operation in the case of the lady with carcinoma of the cervical esophagus, was thought of at the time of operation, and that if he had to do it over again he thinks that is exactly what he would do. However, at the time of operation he had removed the sternocleidomastoid muscle, the right lobe of the thyroid gland, and the strap muscles; and that to have placed a skin graft behind the esophagus it would necessarily have had to be placed directly in contact with the common carotid artery and internal jugular vein, and there was some question in his mind whether a graft would have been successful under these conditions. The ideal arrangement would have been to have had a skin flap from the right side of the neck to cover the artery and vein, and a skin graft from the abdomen to place around the trachea and behind the mobilized esophagus.

The question of pulsion diverticulum of the esophagus, and the type of operation to be employed, comes up every so often, but with the newer chemicals and the newer surgical knowledge of the mediastinum the two-stage procedure will probably be used much less frequently in the future. The first patient upon whom Doctor Watson performed a two-stage procedure had a coughing attack the day following the first operation, so that the violent neck movements tore out the sutures which had been used to hold the sac in the upright position. The wound became infected, and the second stage of the operation was very difficult. Doctor Watson said it was his impression that the two-stage procedure is more apt to be followed by recurrence.

With regard to the question of late radiation effects in these patients with cancer of the cervical esophagus treated by radiation, the patient shown by Doctor Watson at this time is the only one who is alive more than five years. So far, he has not shown any tendency to develop postradiation complications. The other patients treated in this fashion have not lived long enough to develop the complications mentioned by Doctor Lilienthal.

CYSTS OF THE SPLEEN

ROY D. MCCLURE, M.D.
DETROIT, MICH.
AND
W. A. ALTEMEIER, M.D.
CINCINNATI, OHIO

UNLIKE cysts of the ovary, liver, kidney or other abdominal organs, cysts of the spleen are very rare. Only four cases were reported by Pemberton[2] in approximately 800 splenectomies, an incidence of 0.5 per cent. Up to January 1, 1939, Fowler[1] collected a total of 137 reported cases. We have found 11 more reported in the literature,[2-11] up to February 1, 1941, making a total of 148. We wish to report an additional case seen recently at the Henry Ford Hospital.

Cysts of the spleen have been classified as single or multiple, unilocular or multilocular, parasitic or nonparasitic, true or false, primary or secondary, and hemorrhagic, serous, or lymphatic. Most of these classifications are not entirely satisfactory. The following classification (Table I) is a modification of those submitted by Moynihan[12] and Fowler.[13] True cysts of the spleen have a specific secreting lining which may be epithelial, endothelial, or parasitic. False cysts possess only a dense hyaline fibrous tissue wall or a layer of condensation of adjacent splenic tissue.

TABLE I

CYSTS OF THE SPLEEN

I. True cysts—lined by specific secreting membrane:
  A. Epithelial:
    1. Dermoids
    2. Epidermoids
  B. Endothelial:
    1. Lymphangioma
    2. Hemangioma
    3. Polycystic disease
    4. Some serous cysts
  C. Parasitic—lined by protoplasmic matrix containing numerous nuclei
    1. Hydatid cyst caused by ecchinococcus
II. False cysts—no specific secreting lining:
  A. Hemorrhagic
  B. Serous
  C. Inflammatory
    1. Acute necrosis in infection
    2. Chronic tuberculosis
  D. Degenerative liquefaction of infarcted areas caused by embolism or arterial thrombosis

According to Fowler,[1] ecchinococcus cysts occur about twice as frequently as all of the various forms of nonparasitic cysts. False cysts are encountered approximately four times as often as the true type. Eighty per cent of the false cysts are large, solitary, and unilocular; two-thirds being of the hemorrhagic variety, and one-third of the serous type. An additional case report of a large, solitary, false serous cyst of the spleen is presented herewith.

Case Report.—J. S., white, male, age 11, was admitted to the Henry Ford Hospital, March 2, 1940, complaining of pain and fulness in the left abdomen. He had been well until three months previously, when a bulging of the upper left abdominal quadrant was first noted. There was no history of abdominal trauma preceding the appearance of this mass. Two weeks prior to his admission to the hospital, the bulging area became painful, following a blow by the handle of a snow shovel. The past history was essentially negative.

Physical examination revealed a well-nourished, white boy, who did not appear acutely ill. Temperature 99.2° F.; pulse 88; respirations 20. The head, neck and chest

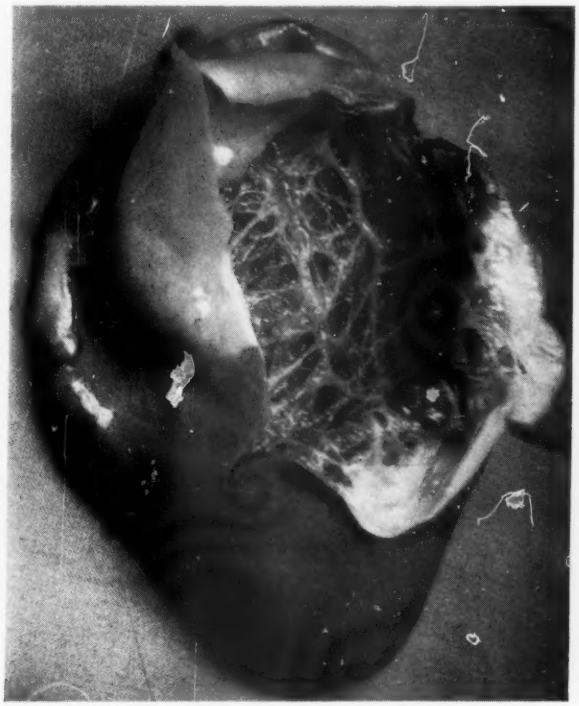

FIG. 1.—The gross appearance of the removed spleen.

were essentially normal. In the left upper quadrant of the abdomen a definite bulging was evident. Percussion note over this area was flat. A large mass was palpated extending inferiorly and medially from beneath the left costal margin. It was smooth, rounded, firm, slightly tender, and moved with respiration. No notch was palpable. Rectal examination was negative. Uranalysis showed no abnormal findings, except a positive reaction for albumin. Hemoglobin 11.7 Gm.; R.B.C. 4,070,000; W.B.C. 5,250. Differential count showed no significant changes. The tuberculin and blood Wassermann tests were negative. A plain roentgenogram of the abdomen showed a large, soft tissue tumor in the left upper quadrant, which extended inferiorly and slightly to the right of the midline. Barium enema examination revealed downward and forward displacement of the splenic flexure of the colon by an extrinsic mass. Pyelograms showed upward displacement of the left kidney.

Operation.—March 7, 1940: A left subcostal incision revealed a large splenic cyst occupying the upper two-thirds of the spleen. It contained 1,620 cc. of straw-colored

fluid. After aspiration of the fluid, the spleen was mobilized by separating its adhesions to the diaphragm and posterior parietal peritoneum. Splenectomy was then performed after division of the gastrosplenic ligament and transfixion of individual vessels in the pedicle by black silk. The patient withstood the operative procedure very well, and his wound healed *per primam.*

Pathologic Examination.—Dr. F. W. Hartmann: The spleen weighs 270 Gm. (after aspiration of contents of cyst), and measures 17.5×12.0×7.0 cm. The lower third of the spleen is of normal consistency with light reddish-brown color, and distinct architectural markings. The upper two-thirds consists of a thin-walled cystic structure, with a maximum diameter of 13 cm. Trabeculations are present within the lumen (Fig. 1). On the cyst wall, enlarged cords of fibrous tissue run in all directions. Microscopic examination of sections of the spleen and cyst wall shows the latter to be devoid of epithelial lining. The wall consists of rather dense, pink-staining, fibrous tissue, beneath which there is considerable bloody extravasation. The adjacent splenic tissue appears normal. *Pathologic Diagnosis.*—Benign simple cyst of spleen.

Discussion.—The solitary nonparasitic cysts of the spleen is the type most frequently encountered by the surgeon. In the series of 137 cases, collected and reported by Fowler,[1] 79 per cent, or 108 cases, were of the false variety. Of these 108, 71 per cent, or 77 cases, were large solitary hemorrhagic cysts, and 29 per cent, or 31 cases, were large serous cysts. The present case falls into this latter group.

The etiology of solitary nonparasitic splenic cysts is still obscure. It has been repeatedly pointed out that too few cases have been reported to justify any extensive conclusions as to etiology. Women appear to be most often affected, particularly during the child-bearing age. Most cases occur between the ages of 20 and 50, although they have been noted in very young children and even in the newly born infant. Trauma seems to play an important rôle in the formation of large hemorrhagic or serous types. Many of these are more properly described as encysted hematomata due to an injury which fails to produce a laceration of the surface of the spleen, but which causes tearing of the vessels in the interior of the organ and gross hemorrhage. If the patient survives, a cyst with bloody-stained fluid and fibrous walls is formed in time. Intrasplenic hemorrhage, however, may also occur spontaneously without antecedent trauma and subsequently form a cyst.

It is believed by some that the complete absorption of blood results in the transformation of a hemorrhagic cyst to a serous type, although it is known that the majority of cases of serous cyst give no history of previous trauma. In Fowler's series only 16 per cent of the serous type were known to have been preceded by trauma.

The signs and symptoms of splenic cyst are not distinctive. Since no apparent function of the adult spleen is known, we are unable to recognize any symptoms attributable to the involvement of the splenic pulp itself. When the cysts are small, there are no symptoms; when they are large, symptoms may result secondarily from adhesions or pressure upon adjacent organs. The chief of such pressure symptoms is pain, characterized by a dragging sense of heaviness in the left hypochondrium and epigastrium. Occasionally the pain may be referred to the left shoulder. Digestive disturbances such as nausea,

vomiting, flatulence and constipation have been frequently observed. Rarely, a twisted splenic pedicle has resulted in collapse. Usually the surgeon is consulted, not because of symptoms, but because of a mass in the abdomen.

The diagnosis of splenic cyst is very difficult. The location of the tumor usually suggests splenomegaly, but the cystic nature is generally not recognized until the organ has been exposed. Cyst of the spleen must be differentiated from other causes of splenomegaly, and cystic disease of the pancreas, omentum, mesentery, left lobe of liver, ovary, or kidney. Roentgenologic examination is of great help. A large soft tissue mass may be seen on the plain film associated with elevation of the diaphragm, bulging of the left lower intercostal interspaces, obliteration of psoas shadow (Ostro and Makover[14]), and, occasionally, displacement of kidney. After a barium meal, the stomach may be seen pushed to the right. Barium enema examination will show downward displacement of the splenic flexure. If a preoperative diagnosis of splenic cyst is made, it must be differentiated from the ecchinococcal type. This differentiation may be possible by the precipitin test of Welch and Chapman, the complement fixation test of Weinberg and Parvu, and the cutaneous allergic test of Casoni.

Treatment.—Only cysts of relatively large size require treatment, and fortunately these are usually readily amenable to surgery. Splenectomy, which gives a mortality rate of only 4 per cent,[1] is the treatment of choice, and is usually possible in the nonparasitic solitary type. Enucleation of the cyst is rarely feasible, but has been accomplished. The difficulty in controlling hemorrhage makes it a more dangerous operation than splenectomy. Marsupialization results in a prolonged postoperative course and should be rarely necessary in this type of cyst. Incision and drainage, in one or two stages, has been performed, particularly in those instances when splenectomy was considered too hazardous or impossible.

SUMMARY

A short discussion of cystic disease of the spleen in general and of false cysts in particular is given. The case history and pathologic description of an additional case of a false serous cyst is reported.

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HEMORRHAGIC CYST OF THE SPLEEN

EDWARD V. DENNEEN, M.D.
NEW YORK, N. Y.

THE SPLEEN is unique in that it is a prominent and predominating factor in a very large number of blood dyscrasias and other pathologic processes and clinical entities.

It is the purpose of this paper to discuss a rare variety of splenic cyst; that is, large solitary hemorrhagic cyst. Cysts of the spleen have been classified by Fowler,[1, 2] as dermoid, parasitic, and nonparasitic cysts. Nonparasitic cysts may be subdivided into: (1) True cysts; and (2) pseudocysts. The true cysts include: (1) Infoliation cysts, which are inclusions of peritoneum—inflammatory or traumatic, small and multiple—may be superficial or deep. (2) Dilatation cyst or polycystic disease of the spleen. (3) Neoplastic types (lymphangioma, hemangioma). Pseudocysts have two subdivisions: (1) Traumatic, which may arise from a hematoma, and are usually large and unilocular (hemorrhagic and serous cysts—so called from their contents). (2) Degeneration cysts arising from secondary changes in infarcted areas from arterial degeneration, or occlusion of blood vessels by emboli with consequent necrosis of the spleen pulp; these are also usually solitary and large. It is with this last mentioned class, that is, pseudocysts, or large solitary hemorrhagic cysts, that this paper deals. These cysts have no true cyst lining. Baccelli indicated that cysts could arise from hematomata, and that a capsule could form about them, with a special inner cell lining, and that, as a result, it would not be possible to distinguish them from lymph cysts into which there had been hemorrhage.

Lubarsch disagreed, and believed that no true cell lining could form in a hematoma of the spleen. The genesis of cystic spleen seems to have no points of analogy to the genesis of cysts of the ovary and kidney. In the absence of tubular structure, true retention cysts do not occur.

That hemorrhagic cysts of the spleen are rare is attested to by Benton,[3] who, in 1932, brought the reported number up to 96. The rarity of this condition is further evidenced by the fact that examination of the records of Bellevue Hospital, from 1904 to date, reveal no case of hemorrhagic cyst of the spleen. The only case at all resembling it was a large lymphangioma. Examination of the Pathology Department and mortuary records at Bellevue revealed, for the period from 1904 to 1940, eight cases of cyst of the spleen. It is interesting to note that during this same period there were 48 cysts of the liver. Of these eight cystic spleens, four showed small multiple infoliation cysts, one, a cavernoma with cyst, one, a small unclassified cyst, one, a small parasitic cyst, and one, a small calcified cyst. A study of the records of St. Vincent's Hospital, during the 30 years prior to 1940, revealed no case of

hemorrhagic cyst of the spleen. In this paper will be presented five additional cases from the New York Post-Graduate Hospital.

In the majority of the cases previously reported, the disease has affected persons in middle adult life—a fairly good argument against congenital origin. About two-thirds were females, so the majority of cases occurred in women during the child bearing age. Monnier explains the predilection for the occurrence during the reproductive period of women, by the fact that the spleen becomes congested in pregnancy, during menstruation, and at the menopause, and subsequently relaxes. Large spleens are more apt to be injured and so we find malaria and syphilis predisposing diseases. The one generally acknowledged factor is trauma, reported in about 30 per cent of the cases.

CASE REPORTS

Case 1.—J. D., female, age 42, married. No present or past history is available at this time except that there was no history of trauma. Roentgenograms, destroyed some time ago, showed a cyst of the left upper abdomen, there being a dense ring of calcified tissue about the cyst. The urine and blood count were normal. On July 1, 1919, at the New York Post-Graduate Hospital, Dr. John F. Erdmann performed a splenectomy for a large, solitary, hemorrhagic cyst. She had an uneventful convalescence, and was discharged on the eighteenth postoperative day.

Case 2.—M. H., female, age 12, gave a history of a fall two years prior to admission, in which fall she struck her left upper abdomen. Her past history included measles and pertussis. On physical examination of the abdomen, one found a mass over one handbreadth below the left costal margin. The urine and blood count were normal. The speaker was present in the operating room when Dr. John F. Erdmann performed, on May 25, 1928, at the New York Post-Graduate Hospital, a splenectomy for a large solitary hemorrhagic cyst of the spleen. The diagnosis made by the pathologist was a "solitary hemorrhagic cyst of the spleen with fibrosis of the spleen and chronic fibrous perisplenitis probably due to trauma." Convalescence was uneventful; she left the hospital on the fifteenth postoperative day. Doctor Erdmann has seen, or heard from her annually for these past 12 years, and she is well.

Case 3.—M. B. T., female, age 28, unmarried, was admitted to the New York Post-Graduate Hospital, with the chief complaints of pain in the right lower quadrant and the left abdomen of one year's duration. Her past history included a tonsillectomy 13 years previously, and frequent attacks of influenza. For one year prior to admission, the patient had had dull pains in the right lower quadrant, varying in intensity, and sometimes absent. She had occasional nausea when tired. There had been occasional pain in the left abdomen, worse following roentgenotherapy five months previously. She had noticed a mass in the left abdomen for 16 years, but no pain or tenderness in that region until one year previously.

The urine and blood count were normal. A large, firm, movable mass could be felt in the left upper quadrant, extending well over to and below the umbilicus. At operation, Dr. John F. Erdmann removed the spleen containing a large, solitary hemorrhagic cyst and a cystic right ovary. This patient had an uneventful convalescence, and was discharged on the twentieth postoperative day.

Case 4.—M. K., male, age 23, was admitted to the New York Post-Graduate Hospital, with the chief complaint of a "mass in the abdomen" of four years' duration. His past history was not remarkable; he had had the usual childhood diseases. The relevant facts of present illness were that four years prior he had noticed a bulge in the left upper abdomen and a small mass, freely movable and not tender. Three months before

hospitalization, he had noted a gradual increase in the size of the mass, so progressive that his vest no longer fitted him. He had no symptoms whatever.

Physical examination revealed a mass four finger's-breadth below the left costal margin; the mass was movabe, lobulated, and felt like encapsulated fluid rather than a solid tumor. The stomach was found pushed to the right. Intravenous urograms showed fairly good left kidney function; the minor calices were not visualized. A retrograde left pyelogram showed the mass to be not part of the kidney, and probably splenic.

Laboratory data indicated normal urine and blood counts; normal nitrogen, chloride and CO_2 combining power blood values; and a negative complement fixation for ecchinococcus.

On October 26, 1932, Dr. C. G. Heyd removed the spleen. There was at the lower pole of the spleen a cyst, containing 2,000 cc. of chocolate-colored material; it was ten inches in diameter; there were adhesions of the omentum and intestine. The pathologist reported "benign cyst of the spleen, hypoplasia of the spleen, no true cyst lining."

Postoperatively, the patient did well and left the hospital on the fifteenth day.

Case 5.—(Author's case): The patient, a male, age 32, was admitted to the New York Post-Graduate Hospital, complaining of intermittent, dull pain in the left upper quadrant of eight months' duration. There was, he said, a feeling of something sticking to the anterior abdominal wall on inspiration, suddenly released on expiration. He complained, moreover, of slight gas eructations.

Twenty-four years prior to admission he had suffered a fracture of the right leg; for ten years he had noticed a prominence in the left upper quadrant, symptomless until eight months prior to his coming into the hospital.

Abdominal examination showed a firm mass in the left abdomen, extending almost to the umbilicus below and medially; medially there was a notch; the mass moved with respiration. Gastro-intestinal roentgenologic studies showed "some diverticula pouching in the pars cardia under the dome of the diaphragm near the midline"; and showed a large extragastric mass displacing and compressing the stomach to the right (Figs. 1 and 2). Intravenous and left retrograde pyelograms showed extrinsic pressure on the left kidney (Fig. 3).

The laboratory reported the urine as having a little albumin, and five granular casts, per high-power field; blood Wassermann was negative; basal metabolic rate was minus one; icterus index seven point nine; hemoglobin 88 per cent, R.B.C. 4,600,000; W.B.C. 3,000 to 6,000, with a normal differential count; and normal fragility of erythrocytes.

On December 9, 1937, a diagnostic splenic puncture was made. Dark green fluid spurted from the needle; this showed innumerable cholesterol crystals.

On December 13, 1937, four days after splenic puncture, under ether anesthesia, the spleen was removed. There was a large cyst at the upper pole. Convalescence was uneventful and the patient was discharged on the thirteenth postoperative day.

Pathologic Report.—Gross: The spleen, which weighs 1,110 Gm., after perfusion and fixation, is enlarged and distorted by a cystic condition of one pole. The cystic area measures approximately 14x13x12 cm. The noncystic portion surmounts the cystic portion, in the manner that the epididymis surmounts the testis. The solid portion has maximum diameters of 15, 6 and 4 cm. (Fig. 4).

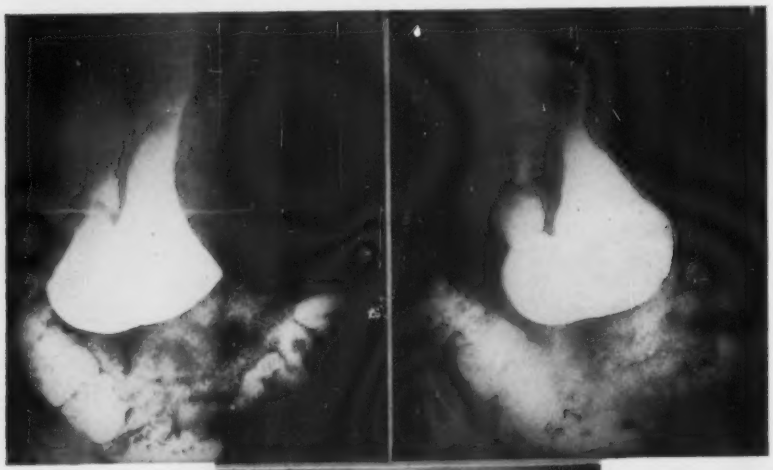
The capsule of the spleen shows distinct confluent areas of gray thickening, particularly over the cystic portion. These stand out in map-like fashion, against the background of normal brown red. At the hilus the vessels are normal in appearance.

On section, about 500 cc. of freely flowing chocolate-colored, slightly frothy fluid escapes. On standing fresh blood settles. The cyst wall has an average thickness of one Mm. for the most part where there is practically no splenic tissue in its wall. At the junction with the unaltered spleen the thickness increases because of the thin lamella of splenic tissue included (Fig. 5).

The cyst wall is the gray tissue of the spleen capsule except where the splenic tissue is noted. The inner lining is shaggy. It is dark brown-red where splenic tissue lines the cyst and slightly dirty golden yellow where the splenic capsule serves as the cyst capsule. There are numerous incomplete septa formed by the fibrinous elements.

The noncystic portion of the spleen is separated from the cystic areas only by the lining of clot already described. This finding further strengthens the belief that the

FIG. 1. FIG. 2.



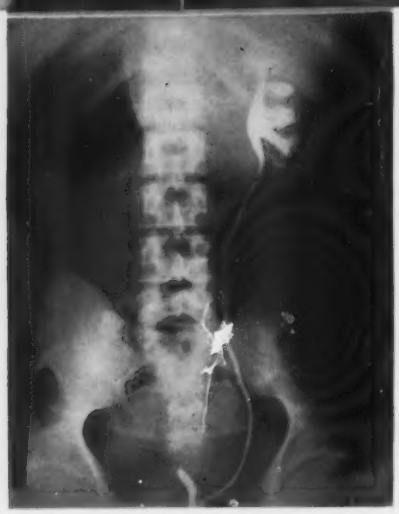


FIG. 3.

FIG. 1.—Roentgenogram showing a mass in the left upper quadrant displacing the stomach to the right and the intestines below.
FIG. 2.—Oblique roentgenogram showing the mass in the left upper quadrant and the displacement of stomach and intestines.
FIG. 3.—Left retrograde pyelogram showing an essentially normal left kidney.

major portion of the wall of the cyst is the splenic capsule and that the cyst probably arose as a result of a breakdown of a large hematoma.

Microscopic.—The unaltered portion of the spleen is free of blood, because of the perfusion fixation. There is normal delicate structure to the sinuses which are lined by endothelial cells. There are no signs of sclerosis either in the capsule in such areas or in the splenic arteries or arterioles.

The capsule of the spleen can be traced outward where it forms the wall of the cyst. Here the cyst is lined by a layer of eosinophilic amorphous material in which there are numerous spear-shaped spaces, cholesterol crystals.

In those portions of the cyst where the wall is formed by the adjacent spleen the cholesterol crystal-bearing amorphous material is in part replaced by granulation tissue which is separated by more mature connective tissue from the spleen proper. Many of the cells of the granulation tissue are swollen, with fine light yellow-brown material, phagocytized lipids. Fresh areas of hemorrhage are also noted in the granulation tissue. *Pathologic Diagnosis:* Cyst of spleen apparently resulting from breakdown and organization of repeated hemorrhages.

This patient has been seen every few months since operation. He is symptom-free and well. Blood counts, made every three months, have been normal, averaging a hemoglobin of 90 per cent, R.B.C. 4,800,000; W.B.C. also normal; the blood smears are normal.

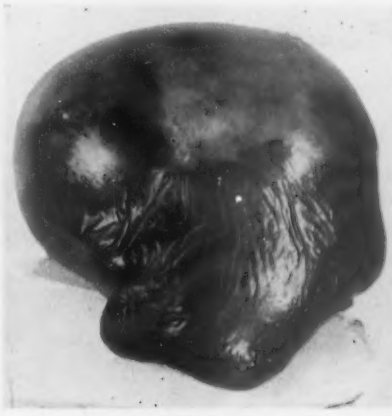


FIG. 4.—Left lateral view of the spleen.

FIG. 5.—View of the cut spleen showing the large cyst in the upper pole. The cyst is about one-fifth the size before decompression.

SUMMARY.—The clinical picture of these five cases is strikingly similar; namely, a firm mass in the left upper quadrant, extending to the midline and down to the umbilicus, the general health and condition of the patient unaffected; some discomfort in the left upper quadrant and moderate indigestion; rather normal blood counts with no evidence of any blood dyscrasia; gastro-intestinal roentgenograms, when made, showing an extragastric mass pressing the stomach to the right; left pyelogram showing no intrinsic kidney lesion.

Five cases of solitary, large hemorrhagic cyst of the spleen are reported. All presented the same clinical picture and all were cured by splenectomy.

My thanks are due to Doctors Erdmann, Heyd and Symmers for use of material.

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Discussion: Dr. Charles Gordon Heyd (New York): On June 26, 1939, I reexamined the fourth case quoted by Doctor Denneen, and found the patient in excellent health, with a firm abdominal cicatrix.

Dr. Royal H. Fowler, and from whom I quote freely, in March, 1940, made his latest contribution on cystic tumors of the spleen (International Abstract of Surgery, Surg., Gynec., and Obstet., 70, No. 3, March, 1940). From the first cystic tumor of the spleen, a dermoid reported by Andral, in 1829, to January 1, 1939, Fowler reports from the literature 137 nonparasitic splenic cysts, 21 per cent being primary or true cysts, and 79 per cent secondary or false cysts. Doctor Denneen now adds five additional cases, three of Dr. J. F. Erdmann, one of Doctor Heyd, and one by himself. It is obvious that there must be a considerable number of unreported cases—occasions where the surgeon encounters one case and does not report it. In any event, solitary cysts of the spleen are uncommon when compared with the incidence of parasitic cysts (echinococcus 2 per cent in the spleen) or with cysts of ovary, liver or kidney. Secondary splenic cysts (79 per cent) are about four times as frequent as primary cysts (21 per cent).

Polycystic disease, lymphangiomata and hemangiomata constitute 62 per cent of the 21 per cent of primary, true splenic cysts, the remaining 38 per cent being dermoid and epidermoid cysts. Eighty per cent of the secondary or false cysts are large solitary hemorrhagic cysts, as indicated by Doctor Denneen. Of these, 35 per cent lie deep within the interior of the spleen and 65 per cent somewhat subscapular.

Various theories have been advanced to account for hemorrhagic cysts of the spleen, *viz.*:

(1) Effect of menstruation and pregnancy: Seventy per cent of the splenic cysts that occurred in pregnancy were large, solitary hemorrhagic cysts. Fowler believes that the most rational explanation of the development of cysts of the spleen following pregnancy is that infarcation and secondary hemorrhage with cyst formation follows an embolism.

(2) Trauma is an alleged factor in 25 per cent of the cases: Eighty per cent of the cases in which trauma was elicited had large, solitary hemorrhagic cysts.

(3) Antecedent disease: Malaria present in 74 per cent of all of Doctor Fowler's series; 11 per cent had syphilis; and 52 per cent associated with previous disease had a unilocular cyst with hemorrhagic contents.

Thus trauma and antecedent disease, one or the other, or both, were noted in the history in all the cases of unilocular hemorrhagic cyst of the spleen.

URINARY EXTRAVASATION (PERIURETHRAL PHLEGMON)

A CLINICAL STUDY OF 32 CASES

EDWARD O. FINESTONE, M.D.

NEW YORK, N. Y.

FROM THE SURGICAL SERVICE OF DR. JOSEPH B. STENBUCK, HARLEM HOSPITAL, NEW YORK, N. Y.

IN A previous communication[5] the anatomy, bacteriology, and pathogenesis of urinary extravasation were reviewed. The superficial perineal pouch of Colles,[4] in cadavers, was injected with radiopaque colored fluid, the amounts and pressures were recorded, and, subsequently, serial roentgenographic demonstrations and dissections were made. The following conclusions were derived from these studies and experiments:

(1) Anatomically, Colles' fascia is so disposed as to allow of a progressive urinary infiltration of the perineum, scrotum, penis, groins, and anterior abdominal wall.

(2) Injection experiments reveal that the clinical appearances can be simulated (with the exception of penile and abdominal involvement) by using pressures and amounts of fluid comparable to those expected on voiding.

(3) Urine alone does not suffice to produce the clinical pictures.

(4) Other factors are operative in the living subject, namely, (a) the presence of bacteria; (b) the tonicity, contractility and elasticity of the tissues; and (c) an active circulation.

(5) Injection experiments demonstrate the ease with which the vascular tree is inadvertently entered.

(6) The close proximity of the vascular tree to the urethra permits of the easy development of vascular thrombosis or pressure phenomena from encapsulated fluid or abscess.

(7) Vascular thrombosis or infectious thrombophlebitis probably accounts for the frequency of rapid swelling of the genitalia, rapid gangrene, severe toxemia and jaundice.

(8) Injection experiments controlled by roentgenography and dissection, together with clinical and autopsy records, fail to show any case wherein the tunica vaginalis testis is involved by the extravasation.

Anatomic study reveals that all periurethral inflammations must penetrate the very vascular bulb or part of the spongiosum to reach the superficial perineal pouch. In this passage, from urethra to fascial space, they invariably involve the vascular tree, thereby easily setting up thrombosis or thrombophlebitis. Anterograde or retrograde extension of this process is favored by the contractions of the bulbocavernosus and external sphincter muscles, which are brought into play with each act of voiding. This explains the paradox wherein the condition of extravasation is aggravated in those cases which continue to void. Moreover, this concept of the pathogenesis explains the

development of extravasation or periurethral phlegmon without stricture or obstruction; and also the urgent necessity for diversion of the urinary stream, irrespective of whether the patient is voiding well or not. These muscles must be put at absolute rest to prevent them from squeezing the thrombosed bulb, and thereby propelling the process into the scrotal and penile vessels.

On the other hand, according to the hydrostatic theory for the production of urinary extravasation, diversion of the urinary stream was practiced to prevent more urine from being squeezed out into the tissues through a defect in the urethra. This concept is not as sound as the former explanation. In accordance with this latter premise, many surgeons and urologists have failed to divert the urinary stream in cases which were voiding well, or which presented no stricture. The omission of urinary diversion has led to an unwarranted and high mortality.

Once extravasated urine, blood, or an abscess occupies the superficial perineal pouch, it is easy to see how the pressure of the mass in the confined space would produce vascular obstruction of the scrotal vessels without actual thrombosis. This mechanism is seen in many periurethral abscesses. When the abscess is incised, the edema disappears, because of the release of pressure. This process is exemplified in Figure 4.

CLINICAL ASPECTS

Etiology and Symptoms.—At the Harlem Hospital, New York City, most of the patients are Negroes. The high incidence of gonorrhea, with its complications of stricture and periurethral abscess, neglect, and unwarranted and unskillful instrumentation, are the factors which combine to make extravasation more common than in other institutions.

TABLE I

RACE AND AGE INCIDENCE

Total number of cases	32
Number of white patients	4
Number of colored patients	28
Average age of all cases	44.7 yrs.
Average age of 16 survivors	39.3 yrs.
Average age of 16 fatal cases	50.2 yrs.

TABLE II

FACTORS IN ETIOLOGY

	Number of Cases
History not obtained	4
No genito-urinary symptoms, voiding well	6
Stricture of urethra found by instrumentation, operation or autopsy	19
Urethral instrumentation for stricture, urinary retention or urethral stone	9
Trauma other than urethral instrumentation	2
Urethral stone removed by external urethrotomy	1

When a patient with extravasation is admitted to the hospital, the chief complaints are usually referable to toxemia. Chills, fever, malaise, and prostration are the symptoms which cause the patient to seek admission; and the

local signs and symptoms may be so minimal, that valuable time is often lost before the true nature of the condition becomes evident. As the toxemia increases, and especially when there is associated urinary retention, hiccough, disorientation, delirium, and stupor, coma rapidly supervenes. These cases commonly present icterus, which was present in eight of our series of 32 cases.

The most important factor in etiology was stricture, which was found in 19 cases of this series. Nine cases had had urethral instrumentation, two cases suffered trauma other than urethral instrumentation; and one case had a urethral stone. Six cases were voiding well and presented no genito-urinary symptoms on admission.

Of 20 wound cultures two were negative; and 11 presented mixed organisms which were found in the following incidence:

TABLE III

BACTERIOLOGY

Type of Organism	Number of Cases	Lived	Died
Gram-positive cocci	8	3	5
Staphylococci	7	6	1
Streptococcus *gamma*	1	1	0
Nonhemolytic streptococcus	1	1	0
Gram-positive bacilli	1	0	1
Gram-negative bacilli	4	2	2
Bacillus coli	6	3	3
Bacillus proteus	2	1	1
Gram-negative diplococci	1	0	1
Gonococci	1	0	1

Of the 32 cases analyzed blood cultures were negative in 15 cases, of which eight survived and seven died. There were two positive blood cultures: Case 21 presented *B. coli* and pneumococcus; and he died. Case 26 presented streptococcus *beta*; and he survived.

Although a history of antecedent gonorrhea, with frequency, dysuria, urgency, and gradually diminishing urinary stream, may be elicited in rational patients, all of these symptoms may be absent in insidious cases. Careful questioning usually elicits a history of long-standing urethritis or stricture. Superimposed upon either of these two conditions, one finds the situation recently altered by the advent of periurethral abscess or trauma incident to urethral instrumentation or "straddle" injury. However, the onset of periurethral abscess may be very insidious; and not until it is associated with urinary retention, severe toxemia, or frank extravasation is the patient forced to enter the hospital.

According to the hydrostatic theory for the production of urinary extravasation, the following explanation is advanced for the paradox that the worst cases encountered are those who continue to void: (a) Attention is not directed to the necessity for diversion of the urinary stream, because of the absence of retention. (b) If abscess, stricture, or rupture of the urethra produces complete retention, extravasation may not occur (and diversion is practiced early). (c) However, when abscess, stricture, or rupture of the urethra

does not completely shut off the urinary stream, extravasation may occur; and the increased hydrostatic pressure necessary to overcome the obstruction may force urine into the tissues at the site of the defect in the urethra.

Cystometrically, the normal expulsive pressure on voiding has been found to be between 60 and 80 Mm.Hg. With irritative lesions, a hypertonic bladder is characteristic, and the pressure on voiding still higher. The pressure required in most of the injection experiments was usually also between 60 and 80 Mm.—so that the hydrostatic theory for the infiltration of the superficial perineal pouch and the scrotum seems to be confirmed.

Since the patient has been straining for a long period of time, he may not be aware of any added effort. He may not complain of any urinary dis-

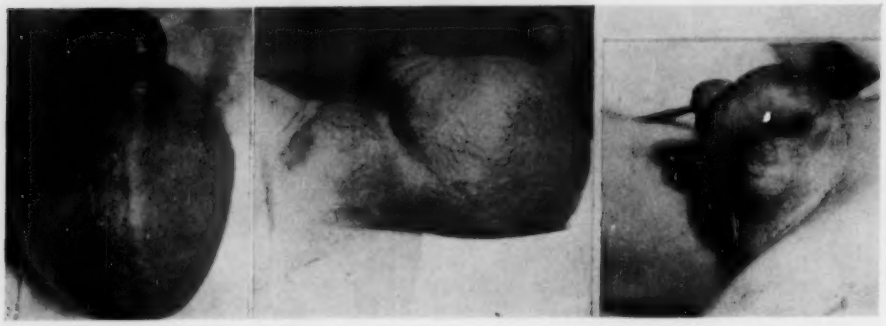

FIG. 1. FIG. 2.

FIG. 1.—Front and side views in a case of extravasation of urine at an early stage of the infiltration of the scrotal tissues. (After Eisendrath and Rolnick). Note the huge swelling of the scrotum which is *symmetrical* and *continuous* with that of the perineal and suprapubic regions.

FIG. 2.—Marked perineal and penile involvement with the scrotum "skipped" in a case of extravasation. Although scrotal involvement is present in this case, it is not as advanced as is usually observed on admission to the hospital. (After Campbell). The swelling of the penis may have resulted from one of three factors: (1) Independent involvement of Buck's fascial compartment; (2) edema from pressure of the perineal mass; or (3) thrombophlebitis.

turbance. It has been the experience of the writer that the most treacherous cases, and those which were most mishandled, were those who continued to void. It did not occur to the surgeons caring for these patients that diversion of the urinary stream was essential to successful treatment. However, this is the most important part of the treatment; and success in handling these cases demands recognition of these facts.

According to the hydrostatic theory, voiding "squeezes" more urine out into the tissues, so that diversion is practiced. However, according to the new concept, voiding "squeezes" the thrombosed bulb or vessels and thereby propels the thrombophlebitic process, so that diversion is practiced to put the muscles completely at rest. Whichever concept we select, the urgent need for diversion of the urinary stream is seen as the most rational part of the treatment.

LOCAL CONDITION AND DIFFERENTIAL DIAGNOSIS

The swelling and inflammatory changes usually spread with great rapidity from an initial tender and edematous swelling in the midline of the perineum, leaving gangrene of the subcutaneous tissues in its wake. One most fre-

quently encounters a swelling in the perineum associated with a continuous, symmetrical swelling of the scrotum and penis; and later, sometimes, involvement of the groins and lower abdomen (Fig. 1). Occasionally, the scrotum is "skipped," when the perineum is the site of a swelling and the penis is markedly swollen as a result of the involvement of Buck's[1] fascia independently of Colles' pouch or as a result of thrombophlebitis or venous compression (Fig. 2).

The swelling in the perineum is usually quite firm, tense, and usually moderately tender. Both perineal periurethral abscesses and extravasations yield fluctuation with difficulty. In extravasation the scrotum and penis are not tense, but pit on pressure and usually present no tenderness. The thickness of the infiltrated scrotal wall precludes adequate palpation of the testes and epididymes. The uninitiated frequently mistake the huge swelling of the scrotum to be the result of epididymitis. There really should be no confusion, for in the latter condition, this organ is usually easily palpated and very tender. When the epididymes are obscured by inflammatory hydrocele, the tenseness and lack of involvement of the scrotal wall are evident.

In late cases there is enormous swelling of the scrotum and penis with edema, bogginess, dusky redness, weeping and desquamation of the superficial layers of the skin. Finally, irregular black patches of skin with occasional frank crepitation make their appearance. Sir Benjamin Brodie[2] is quoted as remarking: "In extravasation a black patch on the glans penis is a harbinger of death."

DIFFERENTIAL DIAGNOSIS

Urinary Extravasation	*Periurethral Abscess*
1. Rapid, progressive spread	1. Slow enlargement and tendency to confinement
2. Tendency toward symmetry	2. Tendency toward asymmetry
3. Poorly defined limits	3. Well-marked limits
4. Pits on pressure	4. Induration and tenseness
5. Minimal tenderness except in perineum	5. Well-marked tenderness
6. Exploratory puncture may reveal any type of fluid in perineum, depending upon the cause	6. Exploratory puncture reveals pus
7. Marked toxicity, with high incidence of jaundice	7. Mild toxicity

Both conditions may coexist, and frequently extravasation begins as a periurethral abscess.

Since both conditions require incision and drainage, the differential diagnosis is academic except for the urgency of diverting the urinary stream. Moreover, some periurethral abscesses, associated with urinary retention, are best treated by the addition of an external urethrotomy or suprapubic cystotomy.

TREATMENT

Operative intervention is essential, and always an emergency procedure. Besides multiple incisions into the infiltrated tissues, diversion of the urinary stream is of paramount importance. In various institutions, and at the Harlem Hospital, diversion of the urinary stream has been accomplished by one of three methods: (1) Suprapubic cystotomy. (2) External urethrotomy. (3) Indwelling catheter.

In the experience of the writer suprapubic cystotomy is most preferable because (1) it most effectually drains the bladder; (2) it reduces trauma during the acute infection to a minimum; (3) it puts the bulbocavernosus and external sphincter muscles completely at rest; (4) the tube is most easily cared for and kept patent; and (5) it is followed by perineal fistulae least often.

Perineal urethrotomy, to be correctly performed, requires the passage of a sound, or guide, upon which the urethra is incised. In a very toxic patient with a urethral canal already inflamed and obstructed, and possibly surrounded by abscess or thrombophlebitis, trauma and shock are added by the passage of an instrument. Thereby, thrombophlebitis, bacteremia, pyelonephritis,

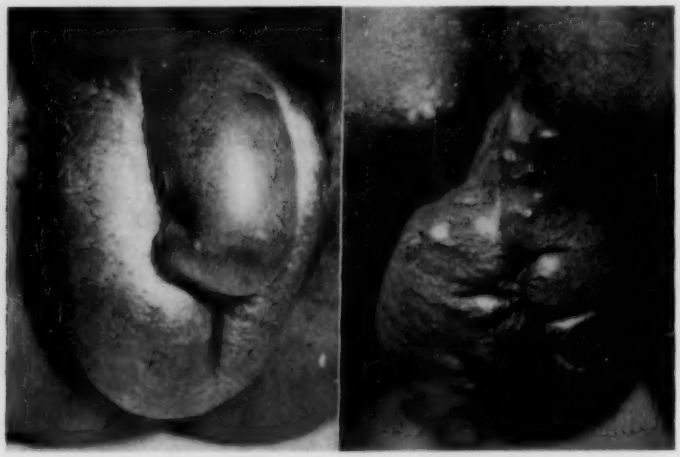

FIG. 3.—Two views of a case of *chronic* extravasation of urine. Note the enormous edema of the penis and scrotum in the anterior view and the multiple fistulous openings as seen in the view from behind. (After Eisendrath and Rolnick.) This type of swelling probably results from either the pressure of a perineal abscess of low virulence or chronic thrombophlebitis.

undue urethral hemorrhage, or rupture of the urethra may be induced. Frequently, patients with extravasation have not been circumcised. The prepuce is so edematous and infiltrated that it cannot be retracted to expose the external meatus. In this event urethral instrumentation cannot be accomplished until after a dorsal slit has been made. The latter requires either spinal or general anesthesia, only to be followed by the problematic successful passage of urethral instruments.

This period unduly delays the operation, since one cannot foretell whether he will ultimately operate suprapubically, with the patient supine, or perineally, with the patient in the lithotomy position. This prolongation of anesthesia and manipulation is obviated by performing suprapubic cystotomy. In cases with extensive infiltration of the anterior abdominal wall, it is conceivable that infection might be carried deeper into the fascial planes or space of Retzius by suprapubic cystotomy. Perineal urethrotomy with multiple incisions of the infiltrated tissues would be preferable in these cases.

External or perineal urethrotomy appears to be an easy and simple procedure, especially since another incision is not added to the perineal incisions necessary to drain the extravasation at this site. There is no doubt that the bladder can be effectually drained and the urinary stream diverted in this manner. However, as already indicated, (1) it requires unnecessary and

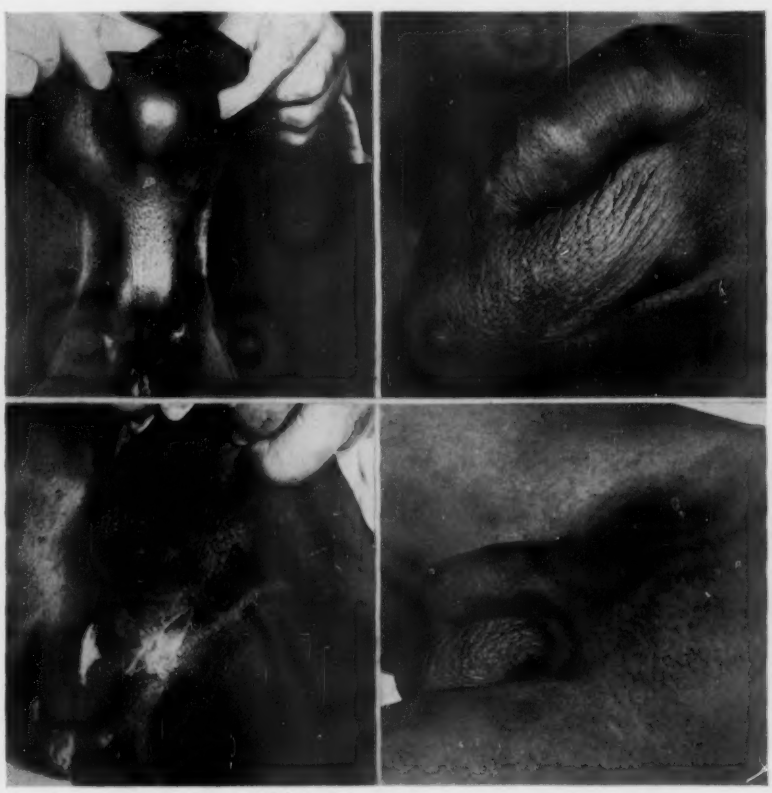

FIG. 4.—(A) and (B) are perineal and side views of a case of periurethral abscess, with edema of the dependent portion of the scrotum, the root of the penis, and the left groin. Note the lack of continuity between the perineal and scrotal swellings, and the asymmetry of the scrotal and penile swellings. The two white scars represent drainage sites of preexisting ischiorectal abscesses, unrelated to the perineal abscess.

(C) and (D) are perineal and side views of the same patient one week after incision and drainage of the perineal abscess. The initial swelling of the scrotum, root of the penis, and groin disappeared three days after operation, without incising any of these edematous structures. The edema in this case, obviously, was due to the pressure of the abscess. This type of case is sometimes confused with actual extravasation in which the infiltrated tissues require incision.

harmful manipulation of the diseased urethra; (2) it does not so effectually put the urethral muscles at rest; (3) it is technically difficult with impassable strictures without a guide; (4) the tube is not so easily cared for postoperatively; and (5) it is followed more frequently by perineal fistulae. The defects resulting from the combination of disease (periurethral abscess, stricture, and phlegmon) and the incision of the urethra are so great that they

make a very serious loss in the continuity of the canal. After the extravasation has been controlled, the patient stabilized, and the urethrotomy tube removed, a prolonged period of hospitalization is required by the manipulation and the use of indwelling urethral catheters in an attempt to heal the perineal fistula. Campbell[3] reports the necessity for five secondary suprapubic cystotomies as part of the plastic repair of these perineal fistulae.

Catheter drainage would seem feasible in those cases where the instrument could be easily passed into the bladder. But, as heretofore mentioned, those cases are the worst in which the patient persists in voiding and the canal is not completely obstructed either by disease or spasm of the sphincters. In a clean traumatic rupture of the urethra extravasation might be prevented by the use of an indwelling catheter; but once infection or extravasation has developed, the use of the catheter should be condemned: (1) In the presence of so much infection the catheter only aggravates the urethritis. (2) It is difficult to keep in place or patent. (3) It cannot be attached to the swollen and infiltrated penis. (4) It moves and loses the optimum site for drainage of the bladder, and urine is either retained in the bladder or forcibly expelled alongside the catheter—to aggravate the extravasation. (5) The presence of the catheter may induce prostatitis, seminal vesiculitis, epididymitis or thrombophlebitis. (6) It does not put the urethra at rest. (7) It results in the highest mortality.

We have seen cases of periurethral abscess incised and drained to be followed by extravasation in a day or two. Some members of the staff, unaware of the necessity for diversion of the urinary stream, have added secondary incisions and revisions to the progressively infiltrated areas, without improvement. But when the floor of the urethra spontaneously broke through, creating a large perineal fistula, the patient immediately began to improve. Unfortunately, this mode of progress is not common when extravasation complicates periurethral perineal abscesses. But perineal fistulae do frequently follow these abscesses after incision or spontaneous rupture, thereby accounting for the ultimate improvement of the cases wherein multiple incisions are made without diverting the urinary stream.

TABLE IV

RESULTS OF OPERATIONS

Type of Procedure	Total Number of Cases	Number of Survivors	Number of Fatal Cases	Percentage Mortality	Hospital Days of Survivors
No operation	3	0	3	100%	
Suprapubic cystotomy, with multiple incisions	11	7	4	36%	48.6
External urethrotomy, with multiple incisions	9	6	3	33%	56.3
Multiple incisions, without operative diversion of the urinary stream	9	3*	6	67%	

* These 3 cases (Cases 14, 17 and 27) are discussed under PROGNOSIS.

Free incisions and drainage of the tissues involved in the extravasation are uniformly recommended by all writers. Experimental study has stressed

the importance of avoiding the tunica vaginalis testis. This pouch and the testicles are not involved, so that there is no necessity to incise and mutilate these structures. Although Campbell mentions the invasion of the tunica vaginalis testis in only one of his 135 cases, he and his associates continue to employ this procedure. The anatomic distribution of the fasciae, the roentgenographic demonstrations, and dissection of injected fluids, clinical experience, and autopsy records, combine to question the value of this procedure. Figure 5 shows the end-results of a patient treated by this method.

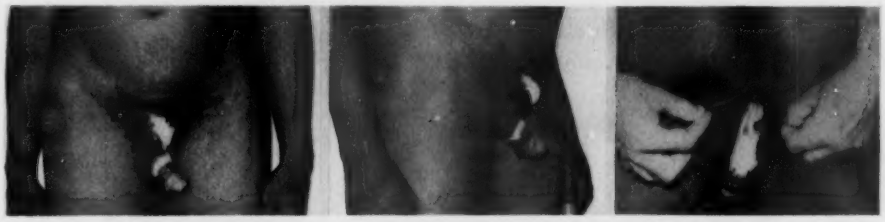

FIG. 5.—Showing the result in a case operated upon at another institution, where the scrotum was bisected, the testes bared and "swung free." Note the extensive scarring, the permanent retraction and elevation of the penis in a distorted position, the absence of the scrotum, the large perineal fistula with the remaining folds of scrotal and perineal skin held apart on either side, and the smaller urethral fistula more distally. The right testicle cannot be palpated. The left testicle is felt beneath the depigmented scar over the external inguinal ring, where it is fixed, tender and atrophied. The spermatic cords can not be felt, and the groins are occupied by long, continuous, adherent scars resembling those following herniotomy.

This patient was operated upon, April 5, 1938, at another institution, where he was confined until July 30, 1938. In spite of hospitalization for 16 weeks, the perineal fistulae remained open. He had been treated as an out-patient until the time this photograph was made (August 9, 1939).

These results may be contrasted with Figure 6, which shows a patient treated by multiple incisions of perineum, scrotum, penis and groins and suprapubic cystotomy, without entering the tunica vaginalis testis.

In making multiple free incisions it is better to leave sufficient skin between the incisions by interrupting them frequently. The presence of small tunnels of skin does not prevent adequate drainage and it greatly facilitates healing. Long, continuous incisions are to be avoided.

The general condition of the patient requires strenuous measures. Continuous intravenous infusions of saline and glucose solutions, transfusions, administration of tetanus and anaerobic antitoxin and gas gangrene serum (although of questionable value), and sulfanilamide are advised.

Spinal anesthesia has given the lowest mortality in the Harlem Hospital series, but the series is too small to come to any definite conclusion.

Postoperatively, frequent wet dressings with warm solution of potassium permanganate, and later, hot sitz baths are used. Careful daily observation of the wounds is required to note whether further infiltration of tissue develops, so that prompt revision, secondary incisions or removal of sloughing tissue may be accomplished without delay. Following control of extravasation, subsidence of fever, and stabilization of the patient, gradual dilatation of urethral strictures is begun. This is most easily conducted while suprapubic drainage is continued. Periodic dilatation and careful follow-up will prevent recurrence.

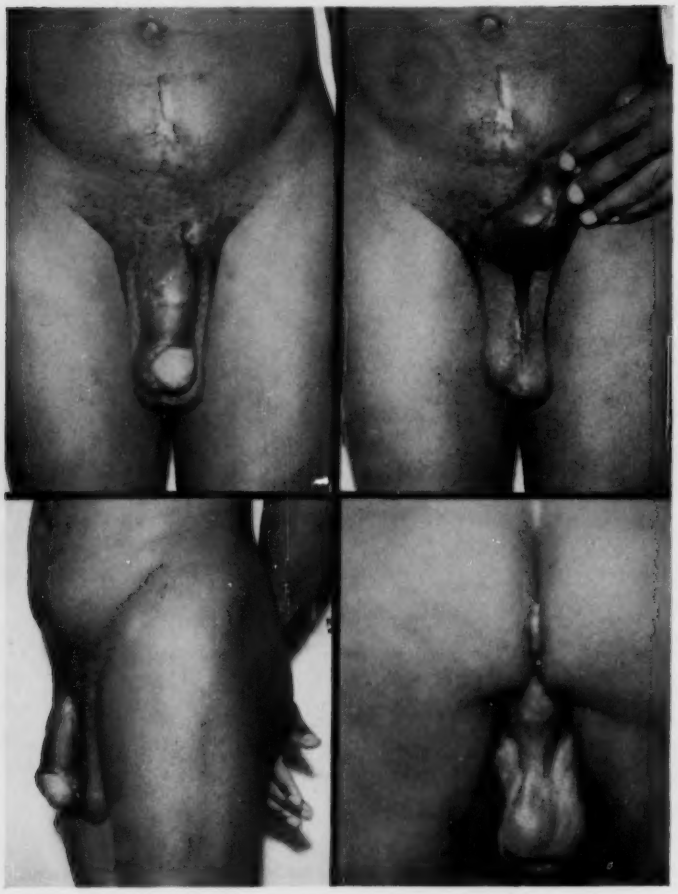

FIG. 6.—Showing the result obtained in a patient (Case 29) who had extensive extravasation involving the perineum, scrotum, penis, groins, and suprapubic region. All incisions were superficial with the exception of those entering the superficial pouch of Colles. The scrotum was not bisected, nor were the testes exposed.

No attempt was made to catheterize the patient, since the penis was tremendously enlarged and edematous with early gangrene of the skin. The prepuce could not be retracted, so that a dorsal slit was made at the completion of the operation.

Under spinal anesthesia, a suprapubic cystotomy was first done through a clear field. Then the perineum was opened though paramedian incisions, followed by multiple superficial incisions through the dartos layers of the scrotum and penis, and through Scarpa's fascia of the groins and lower suprapubic area. Copious amounts of "urinous" fluid escaped from each incision, and the subcutaneous tissues appeared necrotic.

The patient was extremely ill and had a stormy course for a few days, receiving tetanus and gas gangrene antitoxin, three transfusions, continuous intravenous infusions of glucose and saline solutions, sulfanilamide by mouth, and frequently changed wet dressings of warm potassium permanganate solution.

The scarring of the perineum, scrotum, and groins is so superficial that it is hardly discernible. The testes hang normally in a normal scrotal sac. The penis appears somewhat enlarged. Only a small redundant tag of the tremendously edematous prepuce remains following the circumcision performed three weeks prior to photography (August 9, 1939). The suprapubic and perineal wounds are well healed, and there is no urinary leakage from either wound. Prior to the removal of the suprapubic Pezzar catheter, the urethral canal was gradually and easily dilated to No. 30 F. Upon removal of the Pezzar catheter, an indwelling urethral catheter was employed for a few days to facilitate closure of the suprapubic sinus. The patient made a complete recovery, with full restoration of his sexual power, without any disturbance in urination and without any mutilation.

PROGNOSIS

An analysis of 32 cases of extravasation at the Harlem Hospital forms the basis from which the following facts have been noted: Of the 32 cases collected from 1931 to 1939, inclusive, there were 16 deaths. The average

TABLE V

RÉSUMÉ OF 32 CASES OF URINARY EXTRAVASATION

Series from Harlem Hospital, N. Y. C.

Case No.	Days before Admission	Hospital Days before Operation	Days Onset to Operation	Type of Operation: Suprapubic Cystotomy	Type of Operation: External Urethrotomy	Type of Operation: No Operative Diversion	Result	Days in Hospital	Comment
1	10	0	10		+		Lived	33	
2	4	0	4		+		Died	15	
3	7	½	7½		+		Died	3	
4	9	0	9		+		Lived	44	
5	10	0	10			+	Died	1	Multiple incisions only
6	7	1	8	+			Lived	52	
7	4	1	5			+	Died	2	Multiple incisions with catheter
8	2	13	15		+		Lived	44	Slow extravasation following urethrolithotomy
9	10	2	12			+	Died	11	Urethrotomy was unsuccessful
10	5	1	6			+	Died	2	Incision only
11	2	0	2		+		Lived	42	
12	?						Died	1	Moribund on admission. No operation
13	4	0	4			+	Lived	38	Condition limited to penis. Incisions and catheter
14	3	0	3			+	Lived	40	Multiple incisions only. Spontaneous perineal fistula
15	8						Died	1	Moribund on admission. No operation
16	5	0	5	+			Lived	73	Internal urethrotomy 1 mo. before discharge
17	7	0	7	+			Died	2	Extensive extravasation
18	12	0	12				Died	7	Refused operation. Catheter only
19	3	0	3			+	Died	2	Multiple incisions only
20	4	1	5			+	Died	11	Multiple incisions only
21	3	4	7	+			Died	8	Delayed diversion caused death
22	3	0	3	+			Lived	33	
23	6	1½	7½	+			Died	3	Insufficiently wide liberating incisions
24	5	5	10	+			Died	5	Delayed diversion caused death
25	1	11	12		+		Died	15	Delayed operation caused death
26	2	2	4	+			Lived	71	
27	4	10	14			+	Lived	25	Probably only a periurethral abscess
28	7	1½	8½		+		Lived	79	
29	3	0	3	+			Lived	47	
30	4	8	12		+		Lived	96	
31	2	0	2	+			Lived	33	
32	21	1	22	+			Lived	31	Prolonged onset due to periurethral abscess with low virulence

A false impression may be derived from the average statistics of all cases without an intimate analysis. In some cases the process was unusually slow and prolonged, because of low virulence and development from a periurethral abscess. This is illustrated by Case 32, in which 21 days elapsed before admission, and by Case 8, wherein 13 days elapsed in the hospital before the extravasation was incised.

age of the survivors was 39 years, whereas the average age of the fatal cases was 50 years. Three principal factors contribute to the high mortality in extravasation: (1) Delayed treatment; (2) improper surgical management; and (3) severity of infection and toxemia.

Delay in treatment was occasioned both as a result of the ignorance of the patient and the errors of the physician. The circumstances which led to erroneous diagnoses merit emphasis. In many instances both patient and physician were unaware of an initial swelling in the perineum or of any disturbance in the urinary tract. The proportion of cases in which no complaint of pain or tenderness was recorded is remarkable. Another important factor which led to erroneous diagnosis and delay in diversion of the urinary stream, was that the patient continued to void. These factors led to an initial diagnosis of influenza, pneumonia, typhoid fever or brucellosis, with valuable loss of time and the performance of extensive laboratory tests, until the local signs were of such magnitude as to be unmistakable.

Of the 32 cases analyzed, 3 cases were not operated upon, and all 3 died. Of 11 cases subjected to suprapubic cystotomy, 7 survived; and of 9 cases subjected to external urethrotomy, 6 survived. Whereas in the 9 cases operated upon by multiple incisions, without any operative diversion of the urinary stream, only 3 survived. Of these latter 3 cases, which survived without operative diversion, the following explanation is offered: Case 13 presented a condition localized only to the penis and the urinary stream was partly, but inadequately, diverted by catheter. Case 14 developed a spontaneous perineal fistula after multiple incisions, thereby diverting the urinary stream and saving his life. Whereas Case 27 seemed to be only a localized periurethral abscess with thrombophlebitis.

Of the 13 survivors operated upon by suprapubic cystotomy or external urethrotomy, 9 were operated upon on the day of admission; whereas of the 16 cases who died, only 6 were operated upon on the day of admission. Of the 7 cases that died following suprapubic cystotomy or perineal urethrotomy, only 2 were operated upon on the day of admission; the other 5 cases presenting a delay of from one-half to 5 days before operation. Of the 7 cases (Cases 2, 3, 17, 21, 23, 24, and 25) that died following suprapubic cystotomy or external urethrotomy, the following number of days elapsed from onset to operation: 4, 7½, 7, 7, 7½, 11 and 12 days, respectively.

Jaundice appears to be one of the criteria in judging the severity of toxemia, besides the general condition of the patient and the blood chemistry data. Jaundice was present in 8 of the 32 cases. Of the 7 cases that died following suprapubic cystotomy or external urethrotomy, jaundice was present in 4. The 4 other cases with jaundice survived.

SUMMARY AND CONCLUSIONS

(1) A review of the clinical aspects of extravasation into the superficial perineal pouch is offered; with particular reference to the insidious cases and to the differential diagnosis from periurethral abscess.

(2) Emphasis is placed upon the emergency nature of the condition, and the necessity for early diversion of the urinary stream, besides multiple incisions of the infiltrated tissues.

(3) Diversion is indicated irrespective of whether the patient is voiding well or not; and it is preferably accomplished by suprapubic cystotomy in the absence of abdominal involvement.

(4) Avoidance of the deeper structures and the tunica vaginalis testis is stressed as a prevention of unnecessary mutilation.

(5) Of 32 cases reviewed, 16 died. Of 3 cases not operated upon, all died. Of 11 cases subjected to suprapubic cystotomy, 7 survived, and of 9 cases subjected to external urethrotomy, 6 survived. Whereas, of the 9 cases operated upon, without any diversion, only 3 survived. Of the latter 3 cases, two had only localized conditions resembling periurethral abscesses, and the other spontaneously ruptured his perineum, thereby adequately diverting the urinary stream and saving his life.

(6) Of the last 7 consecutive cases treated in the latter part of 1938 and 1939, when the principles enunciated in this paper were emphasized, there were no deaths.

(7) Three principal factors contribute to the high mortality in extravasation: (a) Delayed treatment. (b) Improper surgical management. (c) Severity of infection and toxemia.

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EFFECT OF HEPARIN ON PHAGOCYTOSIS BY THE CELLS OF THE RETICULO-ENDOTHELIAL SYSTEM*

R. H. Rigdon, M.D., and F. S. Schrantz, M.D.

Memphis, Tenn.

From the Department of Pathology, University of Tennessee, Memphis, Tenn

It is necessary to study the effect of heparin on certain of the fundamental processes that occur in the body. Phagocytosis by the cells of the reticulo-endothelial system is one of these processes. von Jansco,[1] in 1931, observed that the cells of the reticulo-endothelial system in the liver, spleen and bone marrow in rats and mice failed to take up colloidal gold during a period of ten minutes if heparin is given previously to the injection of the metal. Rigdon and Wilson[2] recently studied the effect of heparin† on capillary permeability and inflammation. It was shown in these experiments that staphylococci, when given intravenously to rabbits, localize and concentrate in areas of inflammation in the same manner in the animals given the heparin as in the controls. Furthermore, a colloidal dye, when given intravenously, localizes and concentrates in areas of inflammation in a similar manner in rabbits given heparin as in the controls. These two observations appear significant when one considers that both colloids and bacteria apparently localize and concentrate in an area of inflammation as the result of a change in the permeability of the endothelial cells in the small blood vessels.

Another observation made by Rigdon and Wilson[2] is that polymorphonuclear leukocytes apparently phagocytize staphylococci in the subcutaneous tissues of the rabbit in the presence of intravenously injected heparin in the same manner as they do in the subcutaneous tissues of an unheparinized rabbit. It may be possible that heparin has a different effect on the phagocytic activity of the fixed and the circulating cells; however, before such can be stated, additional experimental studies are indicated.

Wislocki,[3] Lang,[4] and others, have studied the fate of carbon particles injected into the circulation. These investigators find carbon particles in the Kupffer cells 30 minutes following the intravenous injection of a suspension of carbon. Intracellular carbon particles are present in the spleen 60 minutes following the injection. Lang[4] states that "the 'endothelium,' or better, the histocytes, lining the sinusoids of the liver, the spleen and the bone marrow, accumulates large quantities of carbon particles immediately following the injection . . . In a majority of the capillaries and capillary veins the endothelium in the earliest stages shows various quantities of unevenly-sized carbon particles, single or in clusters, sticking to the free surface

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† The heparin is "Liquaemin"; supplied by Roche-Organon, Inc.

of the protoplasm." It is suggested by Lang[4] that this phenomenon of phagocytosis is the result of the physical properties of the free surface of the endothelial protoplasm and it is due to a change in the surface tension of the latter.

The present paper is a report of our observations upon phagocytosis of particles of india ink by the cells of the reticulo-endothelial system in normal rabbits and in rabbits given heparin preceding the injection of the ink.

METHODS AND MATERIALS.—Ten adult rabbits are used that weigh between 1.5 and 2.0 Kg. A five per cent saline suspension of Higgin's india ink is prepared immediately preceding the experiment in a quantity sufficient to inject all the animals. Five cubic centimeters of this suspension of carbon are injected into the marginal vein of the ear of five of these rabbits. They are killed 30 minutes later by a blow on the back of the head. Small pieces of tissue are removed from all the viscera and placed immediately in a 10 per cent solution of formaldehyde. The sections are prepared by the paraffin technic and are stained with hematoxylin and eosin

Two cubic centimeters of heparin are injected into the marginal vein of the ear of five rabbits. Each of these rabbits is given intravenously 5 cc. of the suspension of india ink five minutes following the injection of the heparin. Thirty minutes later these rabbits are also killed by a blow on the back of the head. Tissue is removed from the viscera and prepared for histologic examination.

Two rabbits are injected with 2 cc. of heparin in a manner similar to those given heparin and india ink. Blood is removed from the heart 30 minutes later and 0.5 cc. of it is placed into each of four test tubes (0.6x8.0 cm.). The tubes are carefully inverted at frequent intervals to determine the time of clotting. Two normal rabbits are bled in a manner similar to those given the heparin and the blood is observed to determine the clotting time.

Experimental.—Observations on the Clotting of Blood Following an Intravenous Injection of Heparin: The blood from the rabbits given heparin does not completely clot within 18 hours. In contrast to this the blood from the normal rabbits clots in five minutes. One of these two rabbits given the heparin died after approximately two hours. At autopsy, unclotted blood is present in the pericardial, thoracic and abdominal cavities. This hemorrhage apparently has its origin from the cardiac puncture. The second rabbit injected with the heparin is killed after two hours. Unclotted blood is present in the pericardial and the pleural cavities. It appears from these observations that the amount of heparin given to the rabbits is sufficient to demonstrate its effect on phagocytosis by the cells of the reticulo-endothelial system if it should occur.

EFFECT OF HEPARIN ON PHAGOCYTOSIS BY THE CELL OF THE RETICULO-ENDOTHELIAL SYSTEM

Sections from the liver, spleen, adrenal, gastro-intestinal tract, kidney, and lungs are studied microscopically. Carbon particles are present in the

spleen, the liver and the lungs in a larger quantity than in any of the other viscera. It is difficult to study phagocytosis in these sections of the spleen since there are such a large number of carbon particles, and, furthermore, it is difficult satisfactorily to identify each of the phagocytic cells in these sections. Carbon particles are present in the cytoplasm of the cells lining the sinuses of the spleen. They are present both free and in the cytoplasm of the large mononuclear cells in Billroth's cords. The white blood cells in the splenic sinuses have carbon particles within their cytoplasm. The greatest number of carbon particles in the spleen are located apparently in Billroth's cords. There is no difference as far as we can tell in the amount of carbon in the spleen of rabbits given heparin when compared with sections of spleen from the normal rabbits.

The liver is a much better organ than the spleen in which to study phagocytosis by the cells of the reticulo-endothelial system. The Kupffer cells frequently are filled with carbon particles. There appears to be a larger amount of carbon in the phagocytic cells in the walls of the hepatic sinuses surrounding the portal triads than in the cells in any other portion of the hepatic lobule. The cells lining the central veins only rarely contain any pigment. This variation in the degree of phagocytosis by the cells in different portions of the lobule may result from the anatomic location of the Kupffer cells and the point of entrance of the carbon into the hepatic lobule. There is no difference, however, as far as we can tell, in the degree of phagocytosis exhibited by the Kupffer cells in the liver of the rabbits given heparin before india ink and in the rabbits given only india ink.

A large number of the carbon particles are present in the interstitial tissue of the lungs. It appears that this is the primary site for the location of the particles. They are located, however, in the lumen of the small blood vessels in this tissue, and are either free or in the cytoplasm of the circulating leukocytes. Particles are found only rarely in the cytoplasm of any cells in the alveoli. There is no difference as far as we can determine in the number of carbon particles in the lungs of the rabbits given heparin and in the lungs of normal rabbits.

The sections of tissue from the organs other than the spleen, liver and lungs show essentially no carbon particles. There is, however, an occasional mass of carbon in either a glomerular tuft or in the cytoplasm of the cells lining a sinus in the adrenal. The leukocytes in the lumen of the blood vessels frequently have carbon particles within their cytoplasm. The greatest number of such cells are present in the lumen of the vessels in the spleen and the lungs. There is no variation in the amount of carbon present in the cytoplasm of the leukocytes and free within the lumen of blood vessels, in normal rabbits and those given heparin.

The endothelial cells lining the small blood vessels are carefully studied for the presence of carbon particles. There are no particles observed in these cells in either the group of rabbits given heparin or in the group of normal animals.

Discussion.—Particles of carbon are present in the Kupffer cells and in the cytoplasm of the cells lining the sinuses of the spleen in normal rabbits 30 minutes following an intravenous injection of a saline suspension of Higgin's india ink. These findings are similar to those of McJenkin,[5] Wislocki,[3] and Nagao.[6] We did not find any carbon particles in the cytoplasm of the endothelial cells in the small blood vessels.

There is no variation, as far as we can tell, in the amount of carbon in the sections from the group of rabbits given heparin and the controls. Apparently the quantity and the potency of this preparation of heparin is adequate, since the blood did not clot within a period of 18 hours.

Five cubic centimeters of a 5 per cent suspension of india ink is used in these experiments since this amount of ink is phagocytized by only a moderate number of the Kupffer cells within a period of 30 minutes. It is important to give only a small amount of ink in such an experiment, for the cells can phagocytize only a limited amount of materials within a specific interval.

The liver is the tissue of choice in the reticulo-endothelial system to study phagocytosis. Cells lining the sinusoids are the only ones that phagocytize carbon particles. These cells can be easily demonstrated in histologic studies. The spleen, in contrast to the liver, is a very unsatisfactory tissue for the study of phagocytosis of carbon particles. The quantity of ink is marked in the spleen, and, furthermore, the particles are present in both the sinuses and the pulp. It is difficult satisfactorily to identify each of the phagocytic cells.

A consideration of phagocytosis in the presence of heparin is important clinically. If this drug, in the quantity used in cases of thrombophlebitis, should be shown to inhibit phagocytosis of bacteria by either the circulating or the fixed tissue cells, there might be a definite contraindication for its use. The studies of Rigdon and Wilson,[2] and the present experimental observations, indicate that heparin does not inhibit phagocytosis, and as far as we know there are no contraindications to its use in cases of infected thrombophlebitis.

von Jansco[1] observes that 5–10 mg. of heparin when given intravenously to mice prevents the phagocytosis of colloidal particles of gold during an interval of ten minutes. When smaller doses of heparin are given phagocytosis is merely retarded. von Jansco[1] found that "Germanin," a potent anticoagulant, does not prevent the precipitation and the phogocytosis of india ink. He did not study the effect of heparin on phagocytosis of india ink by the reticulo-endothelial system.

It is significant to observe the above variations of the two anticoagulants, heparin and "Germanin," on phagocytosis. It is equally significant to recall that "the reticulo-endothelial elements, while possessing certain properties in common . . . are yet strictly selective and specialized in their activities in the various organs. . . . The endothelial cells of the venous sinusoids are even more indifferent to particulate matter than to soluble dye."[7]

It may be concluded from the experimental studies already made upon heparin that it has no effect upon: (1) The anaphylactic reactions;[8, 9] (2)

capillary permeability[2]; and (3) phagocytosis of staphylococci by polymorphonuclear leukocytes.[2] The results of the present experiment may now be added to these observations; namely, heparin when given to rabbits in a quantity sufficient to prevent the clotting of blood for 18 hours has no effect, as far as we can tell, upon phagocytosis by the cells of the reticulo-endothelial system.

SUMMARY

There is no difference in the amount of carbon phagocytized by the cells of the reticulo-endothelial system in normal rabbits and those given 20 mg. of heparin intravenously, when 5 cc. of a 5 per cent saline solution of Higgins' india ink is injected intravenously five minutes following the heparin, and the animals are killed 30 minutes later. This amount of heparin apparently is sufficient to effect phagocytosis if such should occur since blood from rabbits given 20 mg. of heparin does not clot completely within a period of 18 hours.

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CARDIOCIRCULATORY DYNAMICS IN SURGICAL SHOCK*

RICHARD L. RILEY, M.D., ROBERT H. WYLIE, M.D.,
AND
FRANK B. BERRY, M.D.
NEW YORK, N. Y.

FROM THE DEPARTMENTS OF MEDICINE AND SURGERY, COLUMBIA UNIVERSITY, NEW YORK, N. Y.

IN THE STUDIES to be presented, physiologic observations are made on the circulatory status in man before and after a surgical operation. The changes in hemodynamics, respiratory gases, and various blood constituents are compared to the reported findings in secondary shock in humans.

Shock has proved itself to be such an intriguing and elusive problem that a large number of investigations have been carried out during the past 50 years. How much the understanding of the circulatory changes has been improved by these studies is illustrated by comparing the definition of shock given by Gross,[1] in 1872, with that given by Blalock,[2] in 1940. The earlier writer considered shock to be "the manifestation of a rude unhinging of the machinery of life." Blalock, on the other hand, after narrowing the problem down to hematogenic or secondary shock, states: "The initial and the most important alteration in the circulation is the diminution in the blood volume. This may be due to the loss of fluid which escapes from the body or into the tissues of the body, and there may be a local pooling of blood at the site of injury. The important distinguishing characteristic is that there is general vasoconstriction rather than general vasodilatation as in other types of shock. The decline in blood volume is followed by a decrease in the return of blood to the heart and hence in a decrease in the cardiac output. The development of hemoconcentration or dilution at this stage is dependent upon the relative losses of whole blood and of blood plasma, upon the presence or absence of dehydration and upon other factors. If the volume of the circulating blood continues to diminish, the blood pressure declines even though vasoconstriction is maintained. A continued depression of the blood volume and pressure results in a failure of the constrictor mechanism. All of these changes result in anoxia of the tissues, mainly stagnant in type. This is accompanied by general capillary dilatation, by an increase in capillary permeability, by a general loss of fluid, and by a multitude of other alterations."

While fairly general agreement concerning certain features of fully developed secondary shock has now been achieved, the same cannot be said of the earlier changes occurring before symptoms of shock develop. The relatively slow progress on this aspect of the subject appears in part to be due to

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the fact that satisfactory technics have not been available for use in humans. In the present studies methods have been employed which, we believe, are well suited to the elicitation in man of early changes trending in the direction of shock.

The development of a technic for catheterization of the right auricle in man[3] provides a means of making direct observations on mixed venous blood as it returns from the tissues. Since simultaneous observations on arterial blood are readily available by arterial puncture, the net changes resulting from the passage of blood through the tissues can be noted. In addition, by simultaneous collection of expired air, the cardiac output can be determined by applying the Fick formula. Data on cardiac output and on the pressure in the right auricle and brachial artery provide information regarding cardiac dynamics. Furthermore, data on cardiac output and on the pressure, respiratory gas content, and other constituents of the blood entering and leaving the tissues provide information regarding the influences to which the peripheral blood is subjected. The material which follows represents the application of these technics to patients undergoing a surgical operation.

Choice of Surgical Operation.—During a major surgical procedure several factors, including operative trauma, hemorrhage, other fluid loss, sedation and anesthesia, and nervous stimuli, all influence the resultant circulatory status.[4] In order to compare the circulatory changes in a group of cases, therefore, it is desirable to have these influences comparable in each case. We attempted to obtain such conditions by standardizing the operative procedure and minimizing other factors. All cases underwent a first stage thoracoplasty, performed by the same surgeon. Blood loss was measured. Local anesthesia was used to avoid the systemic effects of general anesthesia,[5] and small doses of sedatives were given as needed to prevent circulatory changes related to emotional stress.[6]

Procedure.—Patients to be studied were prepared for operation in the usual way, and received medication as listed in Table I. Before operation a ureteral catheter was introduced into the right auricle and cardiac output determinations made by ballistocardiographic and direct Fick methods, as described elsewhere.[7] The thoracoplasty was then performed and cardiac output studies repeated postoperatively, without changing the position of the catheter. It remained in place for about two and one-half hours on an average. During this entire time a slow saline infusion was maintained through the catheter. Before, during, and after operation, frequent measurements of pulse rate, respiratory rate, arterial blood pressure, and auricular blood pressure were made. Arterial blood pressure was measured with the sphygmomanometer and auricular pressure with a saline manometer. Roentgenograms of the chest were taken in four cases at the end of operation, in order to relate the level of the tip of the catheter to the zero point on the manometer and thus facilitate correction of auricular pressure readings. In the other two cases, estimates were made based on fluoroscopy, previous roentgenograms, and actual chest measurements. The studies on blood and expired air which

TABLE I

Name	Age	Sex	Nativity	Ht. in Cm.	Wt. in Kg.	Body Surface Area, Sq. Meter	Disease	Operation						Postoper. Course
								Procedure	Medication					
M.M.	33	F	Porto Rico	23.4	48.6	1.43	Pulm. Tbc. Cavity LUL	1st stage thoracoplasty, post. Left R. 1, 2, and 3. 11:00–12:15	Nembutal	0.100	p.o.	7:30	A.M.	Smooth
									Morphine	0.008	h.	8:30	"	
									Scopolamine	0.0003	h.	8:30	"	
									Morphine	0.010	i.v.	11:05	"	
									Pentothal	0.150	i.v.	11:30	"	
C.DiL.	32	F	Italy	24.0	55.4	1.54	Pulm. Tbc. Left fibrothorax	1st stage thoracoplasty, post. Left R. 1, 2, and 3. 9:40–11:15	Morphine	0.010	h.	7:30	"	Smooth
									Scopolamine	0.0004	h.	7:30	"	
									Nembutal	0.100	p.o.	9:00	"	
									Morphine	0.010	i.v.	9:00	"	
J.D.	21	M	U.S.A.	28.0	62.2	1.79	Pulm. Tbc. Mixed Tbc. empyema, left. B–P fistula	1st stage thoracoplasty, post. Left R. 1, 2, 3, and 4. 9:55–11:50	Sod. amytal	0.200	p.o.	7:00	"	Smooth
									Morphine	0.010	h.	7:30	"	
									Scopolamine	0.0004	h.	7:30	"	
									Morphine	0.010	i.v.	10:00	"	
									Pentothal	0.350	i.v.	11:00	"	
N.S.	38	M	U.S.A.	26.0	60.0	1.67	Pulm. Tbc. Cavities RUL and RML	1st stage thoracoplasty, post. Right R. 6, 7, 8, 9, and 10. 10:40–11:45	Nembutal	0.100	p.o.	7:00	"	Smooth
									Morphine	0.015	h.	7:00	"	
									Scopolamine	0.0004	h.	7:00	"	
									Morphine	0.010	i.v.	10:35	"	
J.G.	46	M	Italy	26.0	55.0	1.61	Pulm. Tbc. Cavity RUL	1st stage thoracoplasty, post. Right R. 1, 2, and 3. 9:50–11:30	Nembutal	0.100	p.o.	6:30	"	Smooth.
									Morphine	0.010	h.	7:30	"	Thrombosis basilic vein
									Scopolamine	0.0004	h.	7:30	"	
									Morphine	0.010	i.v.	10:15	"	
									Scopolamine	0.0004	i.v.	10:15	"	
J.C.	26	M	U.S.A.	27.6	82.3	2.00	Pulm. Tbc. Tbc. empyema, right	1st stage thoracoplasty, post. Right R. 1, 2, 3, and 4. 10:05–11:50	Sod. amytal	0.200	p.o.	7:00	"	Smooth
									Morphine	0.015	h.	7:30	"	
									Scopolamine	0.0004	h.	7:30	"	
									Morphine	0.010	i.v.	11:10	"	

1% and 0.5% procaine without adrenalin was used in all cases.

were required for cardiac output determination gave a complete picture of the respiratory gases in the blood and lungs. In addition p_H measurements of the mixed venous and arterial blood were made with the glass electrode in two cases, providing the necessary information for finding the carbon dioxide tension and alkali reserve.[8] At the time of each cardiac output study, additional arterial blood was taken for hematocrit and plasma protein determination. Blood loss during operation was estimated in one case by the weight of fluid lost from the operative site* and in the others by the amount of hemoglobin lost.†[9] The amount of saline given through the catheter was measured approximately.

RESULTS.—The six patients studied were all "good risks," and none of them developed clinical evidence of secondary shock. The significant information describing the patients, the operative procedure, and postoperative course, are listed in Table I. The data on measurements made before and after operation are shown in Tables II, III, IV and V. The more important findings were:

(1) *Cardiac Output.*—Of the six patients studied, cardiac output determinations by the Fick method‡ were satisfactory in four, the blood data being inadequate on J. C., and the checks poor on J. G. (The respiratory quotient [Table II] does not check with the ratio a/b [Table V]). Of the four satisfactory cases, two showed a slight increase in cardiac output after operation, and two showed a decrease.

(2) *Oxygen Intake and Oxygen Arteriovenous Difference.*—J. D. and N. S. showed an increase in oxygen intake as well as in cardiac output after operation. As seen by reference to the Fick equation, the ratio of oxygen intake to cardiac output is equal to the oxygen arteriovenous difference. The arteriovenous difference, therefore, varies directly with the amount of oxygen removed from each unit volume of blood, and inversely with the volume-flow of blood per unit of oxygen used. An increase in arteriovenous difference, as shown by J. D. and N. S., indicates a reduced volume-flow in proportion to the oxygen used by the tissues.

* In this case all surgical materials were weighed before operation and discarded, when soiled with blood or plasma, into a known amount of water. After operation all the surgical materials and the water were again weighed, and the increase considered to be due to fluid lost from the operative site.

† The technic of Gatch and Little for determining hemoglobin loss was modified slightly. Blood-stained sponges were discarded into a known volume of normal saline, and hemoglobin determinations performed on this fluid by the Sahli or the oxygen capacity technic. Grams of hemoglobin lost were readily calculated and translated into terms of cubic centimeters of patient's blood.

‡ Cardiac output in L./min. $= \dfrac{O_2 \text{ intake in cc./min.}}{O_2 \text{ arteriovenous difference in cc./L. blood}}$

or

$$= \frac{CO_2 \text{ output in cc./min.}}{CO_2 \text{ arteriovenous difference in cc./L. blood}}$$

In the satisfactory cases these values checked fairly closely (Table V), and an average of the two values was used.

TABLE II

Name	Time of Study	Ventilation* Rate	Ventilation* Liters/Min.	CO_2 Output† Cc./Min.	O_2 Intake† Cc./Min.	Respiratory Quotient
M.M.	Preop.	20	6.39	139.5	175.5	.793
	Postop.	36	5.96	142.5	190.5	.748
C.DiL.	Preop.	18	5.17	131.0	172.0	.762
	Postop.	26	6.68	151.0	203.0	.744
J.D.	Preop.	22	7.62	181.0	234.0	.775
	Postop.	27	8.62	211.0	265.0	.796
N.S.	Preop.	14	6.34	190.0	182.0	1.045
	Postop.	19	7.14	187.5	251.0	.749
J.G.	Preop.	14	7.06	205.0	263.0	.781
	Postop.	22	7.84	183.5	258.0	.710
J.C.	Preop.		8.47	227.0	305.0	.746
	Postop.		10.00	228.0	320.0	.715

* Saturated gas at 37° C. and prevailing barometric pressure.
† Dry gas at 0° C. and 760 Mm. hemoglobin.

M. M. and C. DiL. showed an increase in oxygen intake but a decrease in cardiac output after operation. On both accounts the arteriovenous oxygen difference increased, indicating, as before, that the volume-flow of blood in proportion to tissue needs was reduced.

(3) *Oxygen Saturation of Arterial Blood.*—The oxygen saturation of the arterial blood was in all cases essentially unchanged after operation, regardless of changes in cardiac output, indicating that gas exchange in the lungs proceded in a normal manner.

(4) *p*H, *Carbon Dioxide Tension, and Alkali Reserve.*—In two cases the blood *p*H was measured, and with this additional information carbon dioxide tension and alkali reserve were determined. One of these cases showed an increased cardiac output after operation and the other a decrease. The blood of both cases was more acid after operation and showed increased carbon dioxide tension and reduced alkali reserve. In the patient whose cardiac output increased, the alkali reserve, although decreasing, remained within normal limits, while in the patient whose cardiac output dropped, the alkali reserve was definitely below the limits of normal.

(5) *Pulse Rate and Stroke-Volume.*—The pulse rate changes bore no consistent relationship to minute-volume of cardiac output. Of the two patients whose cardiac output increased after operation, J. D. showed a marked increase in pulse rate, while N. S. showed very little, and of the two whose cardiac output decreased, M. M. showed a marked increase in pulse rate, while C. DiL. showed very little. The pulse thus gave no clue as to total cardiac output. Since the variations in absolute value of cardiac output were not large, stroke-volume varied inversely with the pulse rate in each case.

(6) *Auricular and Arterial Blood Pressure.*—Patients whose cardiac output increased showed very slight reduction in auricular pressure and only small reduction in arterial pressure. Patients whose cardiac output decreased showed somewhat greater changes. Systolic pressure tended to drop more than diastolic.

(7) *Blood Loss and Saline Gain.*—It so happened that the saline given approximated the volume of blood lost in all cases except M. M. Her fluid

TABLE III

		Mixed Venous Blood							Arterial Blood						
		Carbon Dioxide				Oxygen*			Carbon Dioxide				Oxygen*		
Name	Time of Study	Cont. Vol. %	Pressure Mm. Hg.	Vol. % at 40 Mm. Press.	pH, at 37° C.	Cont. Vol. %	Cap. Vol. %	Sat. %	Cont. Vol. %	Pressure Mm. Hg.	Vol. % at 40 Mm. Press.	pH, at 37° C.	Cont. Vol. %	Cap. Vol. %	Sat. %
M.M.	Preop.	53.2				10.2	14.8	69.9	49.8				14.4	14.8	97.3
	Postop.	51.2				8.3	13.9	59.7	47.0				13.5	13.9	97.1
C.DiL.	Preop.	51.9	42.4	49.0	7.41	12.6	17.2	73.2	49.2	38.9	49.3	7.43	16.2	17.2	94.2
	Postop.	50.0	49.4	43.8	7.31	10.0	16.1	62.1	46.3	43.5	44.6	7.34	15.2	16.1	94.5
J.D.	Preop.	49.9				13.8	19.4	71.1	46.2				18.2	19.4	93.8
	Postop.	45.6				11.9	17.8	66.9	41.7				16.7	17.8	93.7
N.S.	Preop.	58.1	49.0	52.6	7.36	12.2	16.9	72.2	54.3	46.2	52.0	7.39	15.8	16.9	93.5
	Postop.	55.5	50.9	48.5	7.30	9.4	15.5	60.6	51.9	48.1	48.1	7.34	14.1	15.5	91.0
J.G.	Preop.	55.9				13.2	17.8	74.1	53.3				16.7	17.8	93.9
	Postop.	53.6				10.3	16.2	63.6	50.8				15.2	16.2	93.8
J.C.	Preop.	52.5							46.9				19.2		
	Postop.	46.9							42.1				17.6		

* Oxygen carried by hemoglobin, not including that which is in physical solution.

TABLE IV

		Blood Pressure			Plasma			Blood Loss		
			Arterial							
Name	Time of Study	Auricular Mm. H_2O	Syst. Mm. Hg.	Diast. Mm. Hg.	Hematocrit	Sp. Gr.	Protein Gm./100 cc.	Cc.	Method	Saline Infusion Cc.
M.M.	Preop.	39	110	88	35.8	1.0268	6.76	1,200	Total fluid loss from operative site (weighing)	400
	Postop.	3	90	70	32.9	1.0252	6.22			
C.DiL.	Preop.	55	120	65	38.9	1.0261	6.53	360	Hemoglobin loss from operative site (Sahli)	400
	Postop.	43	90	70	41.5	1.0248	6.09			
J.D.	Preop.	57	120	80	48.8	1.0291	7.55	250	Hemoglobin loss from operative site (Sahli)	400
	Postop.	52	100	80	47.2	1.0288	7.45			
N.S.	Preop.	120	118	86	42.8	1.0273	6.94	480	Hemoglobin loss (Sahli)	700
	Postop.	113	105	85	41.1	1.0266	6.70	620	Hemoglobin loss (O_2 capacity)	
J.G.	Preop.	68	140	90	41.8	1.0291	7.55	480	Hemoglobin loss from operative site (Sahli)	400
	Postop.	33	90	60	37.9	1.0278	7.11			
J.C.	Preop.	37	100	70	46.8	1.0290	7.52	270	Hemoglobin loss from operative site (Sahli)	400
	Postop.	0	95	70	43.5	1.0274	6.97			

loss, as measured, exceeded the saline given by nearly 800 cc. There was a considerable drop in auricular and arterial pressures, a marked increase in pulse rate, and a drop in cardiac output in her case. In the other cases blood loss and saline gain could not be related to other measurements.

(8) *Hemodilution.*—Dilution of hemoglobin was indicated by a drop in the oxyhemoglobin capacity of the arterial blood in every case.

Dilution of plasma was shown by a drop in plasma protein concentration in every case.

A reduction in the volume of cells relative to whole blood volume was demonstrated by a drop in hematocrit reading in five cases. The sixth case, C. DiL., showed an increase in the hematocrit after operation.

Discussion.—The direct Fick method of cardiac output determination used in these studies is discussed elsewhere. Because of its theoretic soundness and because of internal checks within the method, it is thought to be the most reliable procedure available for the determination of cardiac output in humans. In addition, it is suitable for studies in which the patient's active cooperation cannot be obtained.

Previous studies comparing cardiac output determinations by the direct Fick method and the ballistocardiograph in normal man, showed that, under the conditions of those experiments and providing certain corrections were made, the ballistocardiograph was surprisingly accurate.[7] It was, therefore, hoped that in the present studies the ballistocardiogram could be checked against the direct Fick measurements before and after surgery. Unfortunately, there were only two instances before and one after surgery in which the tracings were satisfactory. In general the ballistocardiograms could not be used for calculation of the stroke-volume, the form of the tracings being abnormal either because of too rapid pulse rate or because of extraneous vibrations.

Auricular pressures taken during operation showed a downward trend, as reflected in the pre- and postoperative figures. Moment-to-moment variations were slight, except in the case of M. M., who sighed and grunted a great deal. Sighing caused a sudden drop in auricular pressure and grunting a precipitous rise, presumably related to changes in intrapleural pressure. In five patients, the change of position from the back to the side caused an increase of about 50 Mm. of water in auricular pressure, regardless of which side was up; the sixth patient showed a drop of similar magnitude.

In the case of N. S. the recorded auricular pressures were about twice as high as in the other patients. Roentgenograms of the chest showed the tip of the catheter to be unusually low and anterior, raising the possibility that it might have reached the right ventricle.

The respiratory quotient for N. S. was abnormally high before operation. This is not readily explained, since he was in a fasting state and was not markedly hyperventilating. His medication was comparable to that given the other patients, and there was no reason to suspect a drug reaction. The excellent check which was obtained on blood gas analysis (Table V, Ratio

a/b) suggests that the high respiratory quotient represented the true state of the respiratory gases at that time.

In the determination of blood loss from the operative site, the weighing method gave an estimate based on total fluid loss, including plasma, while the other method gave an estimate based solely on hemoglobin loss. The former would be expected to give somewhat higher results, but the large

TABLE V

Name	Time of Study	Pulse Rate	(a) CO_2 A.-V. Diff. Cc./L. Blood	(b) O_2 A.-V. Diff. Cc./L. Blood	Ratio (a)/(b)	Cardiac Output from CO_2 Data L./Min.	Cardiac Output from O_2 Data L./Min.	Cardiac Output Av. L./Min.	Stroke-Vol. Cc./ Beat	Cardiac Index L./Min. Sq. Mi. B.S.
M.M.	Preop.	92	34	42	.81	4.10	4.18	4.14	45.0	2.90
	Postop.	124	42	52	.81	3.39	3.66	3.53	28.5	2.47
C.DiL.	Preop.	112	27	36	.75	4.85	4.78	4.82	43.0	3.13
	Postop.	116	37	52	.71	4.08	3.91	4.00	34.5	2.60
J.D.	Preop.	84	37	44	.84	4.89	5.32	5.11	60.8	2.86
	Postop.	130	39	48	.81	5.41	5.52	5.47	42.1	3.06
N.S.	Preop.	85	38	36	1.05	5.00	5.05	5.03	59.2	3.01
	Postop.	95	36	47	.77	5.21	5.34	5.28	55.6	3.16
J.G.	Preop.	110	26	35	.74	7.89	7.52	7.71	70.1	4.79
	Postop.	94	28	49	.57	6.55	5.26	5.91	62.1	3.67
J.C.	Preop.	68						5.50*	80.9*	2.75*
	Postop.	96						5.46*	56.9*	2.73*

* From ballistocardiogram.

difference in calculated blood loss between M. M. and the other cases is thought to be only in part due to the difference in the technic of blood loss determination. None of the figures can be considered but a rough approximation.

The effects of sedation and anesthesia appeared comparable in all cases except one. M. M., alone, showed signs of apprehension and moderate pain during operation, resulting in wide variations in auricular pressure and respiratory rate. These signs were not present before and after operation at the time when most of the measurements were made. The other patients ran a relatively steady course and gave no evidence of abnormal activity of the autonomic nervous system. All received a number of drugs in small doses as shown in Table I. While this, in itself, was undesirable, it was necessary to insure satisfactory anesthesia and a satisfactory subjective state.

The trends of the determinations made before and after surgery may be summarized as follows:

Regarding cardiac dynamics, the auricular pressure, or filling pressure of the right heart, showed significant diminution in the cases whose cardiac output declined after operation. Arterial pressure, invariably showed a slight to moderate drop. In relation to oxygen intake, cardiac output dropped in all cases.

Regarding the influences to which the blood was subjected in the tissues, the increased arteriovenous difference, increased carbon dioxide tension in the mixed venous blood, decreased alkali reserve, and decreased p_H all im-

plied that there was slowing of blood flow relative to tissue metabolism, suggesting early peripheral stasis.

An attempt to compare these observations with the findings in the literature on secondary shock in man, reveals that cardiac output, auricular pressure, and mixed venous blood studies have not been reported. Indirect evidence of reduced cardiac output includes the finding of reduced blood flow through the hand (Freeman, Shaw, and Snyder[10]), and the repeated clinical observation of collapsed veins, thready pulse, pallor of the skin, and reduced surface temperature. In regard to auricular pressure, Fishberg's[11] finding of a reduced peripheral venous pressure is suggestive: His figures of 10–20 Mm. of water in shock cases are significantly lower than that of 37 Mm. of water, found by Richards, *et al.*,[12] to be the average auricular pressure in normal man. Because of the necessary pressure gradient from the arm vein to the right auricle, it is implied that Fishberg's cases of shock had low auricular pressures, that is, below 10–20 Mm. of water. Indirect evidence regarding the mixed venous blood is provided by Freeman, Shaw and Snyder,[10] who found the oxygen content of the peripheral venous blood markedly reduced in cases of shock. It is probable that the oxygen content of the mixed venous blood is likewise reduced in shock.

Reports of other measurements on secondary shock in humans are available for direct comparison with the findings presented. Arterial blood pressure,[13, 14, 15] p_H,[16] and alkali reserve[16] have generally been found lowered, oxygen saturation of the arterial blood essentially unchanged,[10] and pulse rate elevated.[16] Hemodilution has been noted in association with hemorrhage,[17, 18] but hemoconcentration is generally considered characteristic of secondary shock.[19]

In the literature on human shock, there are, in addition, references to many other types of study, among the more important of which are the determination of blood volumes,[17, 18, 20] and the comparison of hemoglobin concentration in the capillary and venous blood.[19] These procedures, unfortunately, were not included in the present investigation.

The changes noted after operation, in the cases studied, were, in general, similar in direction but less marked in degree than those expected in shock. They represent physiologic alterations occurring in the absence of, but presumably related to, the shock syndrome.

The expansion of this type of study should lead to a better understanding of the progressive changes in shock, and, thus, help to provide more acute diagnostic criteria and more effective therapeutic measures.

SUMMARY

(1) Studies of the cardiocirculatory status before, during, and after thoracoplasty performed under local anesthesia, were made on six patients. Four of the studies were technically satisfactory.

(2) The technics employed included simultaneous collection of mixed venous blood, arterial blood, and expired air, measurement of auricular and arterial blood pressure, and estimation of blood loss and saline gain.

(3) The various determinations derived from these technics showed the following trends: In relation to oxygen intake, cardiac output decreased; auricular pressure and arterial pressure showed a slight to moderate drop; arteriovenous difference and carbon dioxide tension in the mixed venous blood increased; and alkali reserve and p_H decreased.

(4) The relationships of these findings to those expected in secondary shock are discussed.

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BRIEF COMMUNICATIONS

SPONTANEOUS RUPTURE OF A NORMAL HEPATIC DUCT

REPORT OF A CASE

NATHANIEL E. REICH, M.D., F.A.C.P. (ASSOC.)
BROOKLYN, N. Y.

A REVIEW of the literature on the biliary tract fails to reveal the report of any case of spontaneous rupture of normal bile passages. The value of reporting the condition becomes even more apparent when one notes that records of hepatic duct rupture, even from obvious causes, are exceedingly rare.

The site of perforation in the biliary tract occurring from all causes in a group of 90 cases collected by McWilliams,[1] has been 91 per cent in the gallbladder; 4.4 per cent in the common duct; 3.3 per cent in the cystic duct; and 1.1 per cent in the hepatic duct. However, this latter case (Brunner[2]) was not of a spontaneous nature, but was due to the presence of one stone in the ampulla and two stones in the common duct. Freeland[3] reported one of the earliest recorded cases of a ruptured hepatic duct. This was caused by a stone in this duct.

In 1829, Compaignac[4] described the case of a man, age 35, who had received a violent blow upon the abdomen. He did not die until 18 days later, yet autopsy showed a rent in the left branch of the hepatic duct, and six pints of deep-green bile in the abdomen.

Other authors[5, 6, 7, 8, 9] discuss rupture of the gallbladder, cystic and common ducts, but no mention is made of the possibility of hepatic duct rupture.

In this connection, the anatomy of the hepatic duct[10] is worth reviewing very briefly. The two large biliary ducts, one from the left lobe and a larger one from the right lobe of the liver, unite just beyond the transverse fissure to form the hepatic duct. This duct is 20–40 Mm. (three-quarters to one and one-half inches) long with a diameter of 4–6 Mm., descending one-quarter inch to the right and anterior to the portal vein in the lesser omentum to join the cystic duct in the formation of the common duct. The mucosa is of the columnar type and contains branched tubular gland-like structures.

Case Report.—E. M., white, male, age 73, complained of severe abdominal pain of four days' duration, situated in the epigastric region and extending downward. The pain had been continuous. He had vomited at the onset and several times since. For the past few years, he had been suffering from gastric upsets and melena had been passed on several occasions. There was no history of trauma.

The patient denied all previous illnesses, and claimed to have been in good health all his life. He stated that his habits had always been good. Family history was irrelevant.

Physical Examination.—The patient was a well-developed and well-nourished white male, complaining of severe abdominal pain, most marked at the pyloric region. Temperature 100.6° F., pulse 110, respirations 30. There was no cyanosis or jaundice. General examination was essentially negative other than for the abdominal findings. The

entire abdomen had a board-like rigidity, it was painful and tender, and resistant to palpation.

Laboratory findings showed the urine to be negative. Hemoglobin 90 per cent; W.B.C. 12,350, with 84 per cent polymorphonuclear leukocytes, 16 per cent lymphocytes.

Clinical Diagnosis.—Perforated duodenal ulcer and peritonitis.

Operation.—Under ether anesthesia, the abdomen was opened through a five-inch, right rectus incision, beginning at the costochondral angle. Numerous adhesions were encountered, and free peritoneal fluid of a dirty yellow color was present. This had a slightly bloody appearance near the pyloric region. No perforation of the stomach or intestines or other organ was demonstrable, and because of the extremely poor condition of the patient no further manipulation or further exploration was deemed advisable. The peritoneum, fascia and skin were closed in layers, and a cigarette drain was inserted to the pylorus. The patient was very restless and perspired freely following the operation. He expired six hours later.

Autopsy.—The right heart chambers were markedly dilated. The myocardium was of normal thickness and contained a fine, diffuse fibrosis throughout. The endocardium and valves were normal. The aorta and coronary arteries were involved by a moderate arteriosclerotic process. The lungs presented a slight passive congestion at both bases but were otherwise normal. The liver was small, hobnailed externally, and was bathed in some 300 cc. of thin, cloudy, odorless, yellow fluid. On section, it was markedly cirrhotic, and there was a considerable increase of fibrous tissue in the periportal spaces. The gallbladder was normal and contracted, containing no bile. There was a tiny perforation at the middle of the anterior surface of the hepatic duct, about 0.5 cm. wide, through which could be expressed thin, golden bile. All the layers of the duct were of normal thickness and color, and the mucosa was smooth. No stones were found in the liver, biliary tract, peritoneal cavity, or intestinal tract. The cystic and common ducts were normal. The cystic artery showed no thrombosis. The gastro-intestinal tract was free from perforations or other pathology, other than an acute engorgement of the serosa throughout. Several adhesions in the upper abdomen had been tied and severed. The spleen was soft and friable and of normal size. On section, the normal architecture was replaced by a soft pulpy substance. The pancreas was of normal size, shape, consistency and position, and revealed no abnormalities on section. The genito-urinary tract was essentially normal. Except for cirrhotic changes of the liver, microscopy was essentially negative. *Anatomic Diagnosis.*—Spontaneous rupture of the hepatic duct, bile peritonitis, atrophic cirrhosis of the liver, coronary sclerosis, myocardial fibrosis, and acute cardiac dilatation.

Causes for Rupture.—Four explanations for bile duct rupture have been advanced by Newburger,[12] which are presented in modified form:

(1) *Increased Intraductal Pressure,* with bursting at the critical point of distention. This increased pressure is due to mechanical blockade by stones, reflex spasm of the sphincter of Oddi, or both. The critical point, in the cases described, is at the point of operation (*i.e.,* cystic duct stump, or at entrance of supraduodenal tube). Rolleston and McNee[13] feel that in the case of a healthy gallbladder wall, it may be thinned from distention, and rupture may then take place from trauma, or as a result of sudden pressure brought to bear upon the gallbladder by contraction of the abdominal walls in violent straining, coughing, or in the vigorous abdominal contractions during labor.

(2) *Infection* (cholangitis) destroys the mucosa and elastic tissues, weakens the duct walls and lowers their resistance to possible intraductal pressure increases. Wolfson and Levine[9] report three cases of spontaneous rupture of the common bile duct following choledochostomy. In two cases, the duct

contained calculi, while in the third, it was filled with a thick mucoid cast. In these cases, rupture occurred due to a subacute infectious process at the site of the choledochostomy. A similar case has been reported by Bernhard,[14] except that the spontaneous rupture occurred three years after choledochotomy. Newburger[12] adds a case of his own and eight other collected instances.

(3) *Thrombosis* (possibly of the cystic artery) might account for cases in which the perforation occurs widely separated from an area of operative trauma.

(4) *Reflux of Activated Pancreatic Juice* through a common opening of the pancreatic duct and choledochus, with tissue digestion. The anatomic relationship between the common and pancreatic ducts also militates against such a possibility. In this situation fat necrosis should be present. Pure pancreatic juice will not produce fat necrosis unless activated by intestinal juice,[22] and presumably by tissue kinases.

To the preceding explanations may be added five others:

(5) *Stones* overlooked at the time of operation may eventually produce a pressure necrosis of the wall. Although mention is made only of common or cystic duct stones, it is assumed that similar changes hold for hepatic duct stones. This is of greatest importance, since W. J. Mayo[15] found that in almost one-third of the deaths following common duct operation for stones, autopsy revealed that all stones had not been removed. Others[16, 17] have also found in necropsy material, large percentages of stones left postoperatively in the ducts. In perforations of the gallbladder, stones were associated in over 70 per cent of the cases. The point of extravasation may be microscopic. When the ulceration cannot be found on careful examination, Power,[18] and Horrall[19] feel it is strongly possible that a transudation of bile occurs. Power reported three cases of biliary peritonitis in which stones were found, but with the actual point of perforation overlooked. On the other hand, Walters and Snell[20] believe it remarkable that the mucosa of the common duct is changed so little in the majority of cases of stone in the common duct; the natural resistance of this epithelial surface to trauma seems to be high. Nevertheless, ulceration may occur at points where a stone becomes impacted. In spite of the dilatation of the common duct and inflammatory changes in its wall, rupture is rare.

(6) *Indirect Trauma* to the duct from external sources, such as falls, or auto accidents, may result in overstretching and tearing of diseased or even normal bile ducts. Although such cases have been reported occurring in the cystic and common ducts and gallbladder, they have not been mentioned in conjunction with the hepatic duct.

(7) *Direct Wounds* caused by saber, bayonet, and projectiles. Direct wounds may occur also accidentally during abdominal surgery[21] or paracentesis.

(8) *Upward Traction* due to shrinkage of liver (cirrhosis of liver, or acute and subacute yellow atrophy), or the downward pull of the duodenum by adhesions may conceivably produce overstretching and tearing of the hepatic

duct. Although these etiologic factors have not been mentioned in the literature, it is slightly possible that the cirrhosis and subsequent liver retraction, as in our case, might possibly result in a tear, especially if an element of trauma were also introduced. Against this supposition is the chronicity of a cirrhotic process, and the compensatory changes in a gradual elongation of the duct, as well as the mobility of the duodenum. In addition, no such case has been reported in the literature.

(9) Finally, *carcinomatous invasion* of the duct may produce rupture, although other symptoms based on obstruction become evident very early.

SUMMARY

A case of a spontaneous rupture of a normal hepatic duct is reported. The causes for rupture of the biliary tract are considered. A careful search through the literature failed to reveal a similar case.

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COMMON DUCT OBSTRUCTION DUE TO PRIMARY CARCINOMA OF THE CYSTIC DUCT

RESECTION, WITH REESTABLISHMENT OF CONTINUITY OF THE COMMON BILE DUCT

GORDON D. OPPENHEIMER, M.D.

NEW YORK, N. Y.

FROM THE SURGICAL SERVICE OF DR. A. HYMAN, MT. SINAI HOSPITAL, NEW YORK, N. Y.

CARCINOMA of the cystic duct or of the common bile duct at the junction of the cystic duct is rarely amenable to surgical therapy. The patient herewith presented afforded an unusual opportunity to perform a successful radical operation. That the procedure was only palliative in this instance will be noted from the following report.

Case Report.—Hosp. No. 459614: I. A., male, age 57, was admitted to Mt. Sinai Hospital, July 10, 1940, and discharged, September 3, 1940, with the history of having noted dark urine and light stools three weeks preceding admission. One and one-half weeks later, jaundice was noted with itching. There had been no other symptoms except a loss of six pounds in weight. The past history was essentially negative, except for a mild diabetes discovered four years previously, which was easily controlled by diet.

Physical Examination.—The patient was a well-developed and well-nourished, deeply icteric male. The heart and lungs were normal. There was a large, smooth firm mass in the right upper quadrant of the abdomen extending down to near the umbilicus. This was apparently the liver. Blood pressure 126/80. *Clinical Diagnosis.*—Carcinoma of the head of the pancreas, with common duct obstruction.

Laboratory Data.—Hemoglobin 94 per cent; W.B.C. 8,350, with a normal differential. Stools contained no bile, very faint trace of urobilin, and were free of occult blood. The prothrombin time was 80 per cent of normal. Urine: Faint trace of albumin, no sugar, concentrated up to 1,028 and had 2 to 3 plus bile, and urobilinogen 1–10. Blood Wassermann test negative. Blood urea nitrogen 12 mg. per 100 cc., sugar 130 mg. per 100 cc., cholesterol 300, and cholesterol ester 115. The icteric index was 81 and the bilirubin 7.0. The van den Bergh was direct, promptly positive.

Roentgenologic examination of the abdomen showed no evidence of radiopaque biliary calculus.

The patient was prepared for operation with intravenous vitamin K and bilron capsules by mouth. A citrate blood transfusion was administered on the day of operation.

Operation.—Exploratory celiotomy was performed, July 16, 1940, under ethylene ether anesthesia. An upper right rectus incision disclosed adhesions among the omentum, liver edge, gallbladder and peritoneum, which had to be separated before further exploration could be performed. Both lobes of the liver were markedly enlarged, firm, but smooth. The gallbladder was large, tense, contained no stones, and yielded 150 cc. of hazy, white fluid on aspiration, culture of which was negative. In the region of the common duct was an elongated, irregular firm mass with an adherent nodular mass, evidently a malignancy. The head of the pancreas was normal to palpation. The common bile duct was exposed above the neoplasm and found to be dilated. Aspiration of the duct in this area yielded clear faintly yellow-tinged fluid. The difference between the fluids in the common bile duct and in the gallbladder indicated that the obstructive lesion of the common bile duct was evidently blocking the cystic duct. Obviously, a cholecystogastrostomy was not indicated and it was decided to explore the lesion further.

This was done by skeletonizing the common bile duct and portal vein. A walnut-sized node was dissected away from the right lateral aspect of the vein near the duodenum (Fig. 1). The gallbladder was then mobilized, the cystic vessels tied, and the cystic duct, which appeared to be involved by tumor, was mobilized to the common duct. The gallbladder was then used for traction and better exposure. It was then decided to perform a radical procedure and, therefore, the common duct was severed about 1 cm. above the entrance of the cystic duct and, also, at a point below, where it entered the pancreas under the posterior surface of the duodenum. The gallbladder, cystic duct, and 6 cm.

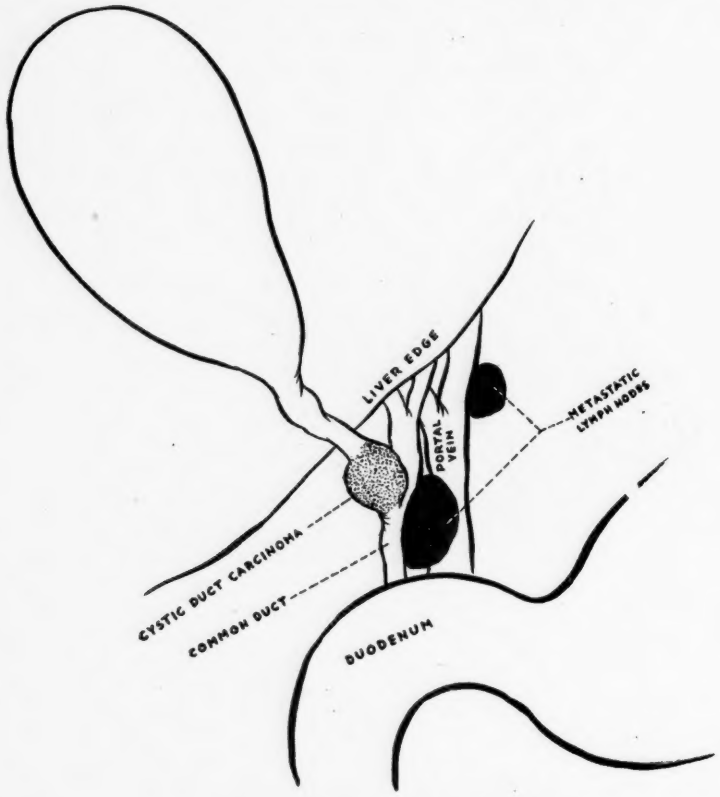

FIG. 1.—Diagram illustrating findings at operation.

of the common bile duct were thus excised *en masse* (Fig. 2). A pea-sized node, which was palpated on the superior mesial aspect of the portal vein, was then removed separately.

A medium caliber T-tube was used for reconstruction. The lower limb was placed for a distance of 1 cm. into the distal stump of the common duct. A purse-string suture was placed around it through the pancreas and duodenum, with a suture through the tube and duct edge to keep it in place. The upper limb of the T-tube was placed into the proximal end of the duct, the cut edge of which reached to the vertical limb of the tube. Interrupted linen sutures were placed between the upper cut end of the duct and the duodenum, which brought the duodenum to it, folding the duodenum around the lower uncovered portion of the T-tube. Two large lappets of omentum were placed around the anastomosed area to further protect it. Iodoform gauze was inserted into the liver bed and a Penrose drain was placed down to Morrison's space. The wound was closed in layers.

Subsequent Course.—The convalescence was uneventful. The T-tube drained profusely and the jaundice became noticeably less as early as two days postoperative. The gauze and Penrose drain were removed on the sixth postoperative day, following which there was some slight, temporary biliary leakage around the tube. The patient was placed on vitamins and bile salts, he received several transfusions, and rapidly regained his strength. On August 28, 1940, 43 days after operation, lipiodol was injected into the

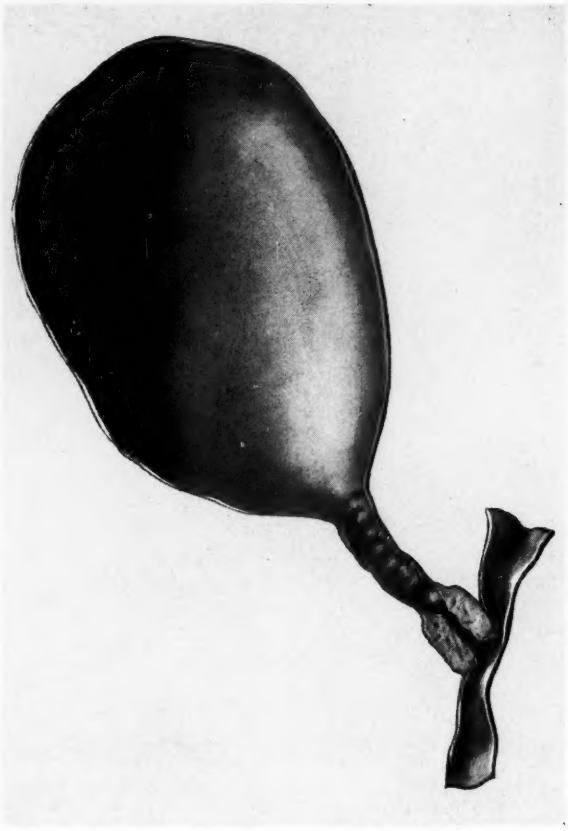

FIG. 2.—Sketch of gallbladder, cystic duct with tumor and common bile duct, which were removed at operation.

T-tube for purposes of making a roentgenologic examination (Fig. 3). This showed that the lipiodol flowed readily into the duodenum. The upper limit of the T-tube filled promptly, and lipiodol passed into the hepatic radicles. The left major hepatic radicle appeared to be moderately dilated. There was perhaps slight dilatation of the right hepatic radicles. The common duct showed a moderate dilatation down to the tip of the lower limb of the tube. Beyond this point the duct was normal in caliber. The distal two inches of the pancreatic duct was filled with lipiodol by retrograde flow.

Following this procedure the tube was clamped off. There was no leakage and the stools were brown. The patient was discharged, September 3, 1940, 49 days after operation.

Pathologic Examination.—Dr. Paul Klemperer, Path. No. 71455: The specimen showed the presence of an adenocarcinoma of the cystic duct with lymph node metastases. The mucosa of the common bile duct was, grossly, uninvolved (Fig. 4).

Follow-Up.—The patient showed a progressive improvement for seven months after operation. He gained in weight and strength and was well, except for a temporary peripheral neuritis of the legs and feet which responded to thiamin therapy. He also had pain in the left shoulder joint due to an arthritis, and roentgenologic examination of it and the spine showed no evidence of metastases. The T-tube was kept closed and undisturbed. There was never any leakage around the tube. His stools were normal and icterus did not reappear. However, after this time, he commenced to slowly deteriorate.

FIG. 3.—Roentgenogram after injection of lipiodol into rubber T-tube. Note prompt flow into duodenum. Portion of pancreatic duct visualized.

At first, anorexia and occasional right upper quadrant abdominal pain appeared. Then weakness became marked, and he spent most of the time in bed. The liver enlarged and became hard and nodular, obviously the site of metastases. The patient became increasingly apathetic and died, June 8, 1941, about 11 months after operation. There was no postmortem examination.

COMMENT.—Primary carcinoma of the extrahepatic bile ducts is, evidently, a rare condition, and carcinoma of the cystic duct is seldom seen at operation. In a recent exhaustive review, Stewart, Lieber, and Morgan[1] collected 27 cases, as instances of primary carcinoma of the cystic duct which were abstracted from the literature. These authors were unable to accept any of these cases, indisputably, as examples of cystic duct carcinoma. It must be remembered that most of these cases were postmortem studies, and, even if the tumor had arisen from the cystic duct, it was not sufficiently localized at

the time of examination to make its origin unquestionable. In the above reported case early operation revealed localization of the primary tumor to the lower end of the cystic duct. In spite of the short history, by the time the tumor had blocked the common duct by extrinsic pressure and angulation, causing jaundice, regional lymph node metastases had already occurred.

That carcinoma of the extrahepatic bile ducts can occasionally be treated by radical surgery is well worth emphasizing, and is the main reason for pre-

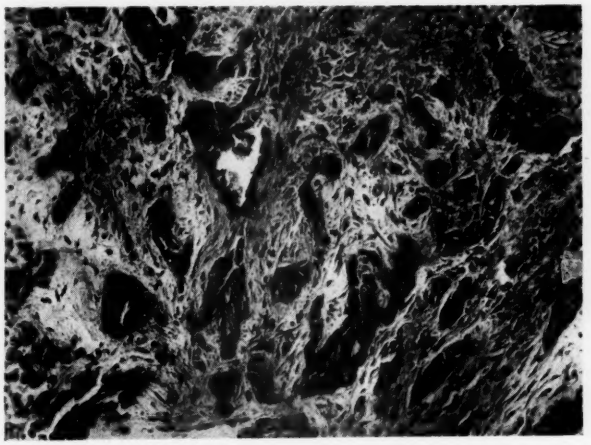

FIG. 4.—Microscopic section of primary cystic duct infiltrating adenocarcinoma.

senting this case. One of the most brilliant of the published cases is that of Garlock.[2] His case was that of a small primary carcinoma of the common bile duct at the entrance of the cystic duct. He was able to resect the gallbladder, cystic duct and a portion of the common duct, and then to perform an end-to-end suture of the common duct over a T-tube. This patient, although desperately ill at the time of operation, recovered and has remained well, without recurrence, for almost three years. A cursory review of the literature indicates that, occasionally, similar successful results have been obtained. Konjetzny,[3] for example, presented a five-week result after radical resection of a common duct carcinoma. Amberger[4] published a one and one-half-year result after resection of a common duct carcinoma, and mentions similar radically operated cases of Kehr and Doberauer. Renshaw[5] found 20 cases of primary carcinoma of the bile ducts in the Mayo Clinic material during the years 1907 to 1921. In two of the cases of cystic duct carcinoma, stones were present in the gallbladder. One of the cystic duct cases was radically and successfully operated upon, with anastomosis of the common duct over a T-tube, and lived for three months.

Of particular interest in relation to the subsequent management of the rubber T-tube is a case reported by Moschcowitz,[6] in 1912. While extirpating an acutely inflamed gallbladder with stones, he found a carcinoma of the common duct and resected it. A reconstruction was accomplished over a T-

tube, using the hepatoduodenal ligament and duodenum for covering the tube. However, he removed the T-tube on the twenty-fifth postoperative day, and a biliary fistula resulted. The case was presented before the New York Surgical Society at an early date, and the question was raised as to the necessity of performing a hepaticoduodenostomy. The T-tube in the present case was left severely alone. No untoward symptoms resulted, and it is evident that, unlike drainage tubes which are left in the urinary tract, encrustations do not form. Undoubtedly, the tube acted as a safety valve preventing obstruction from local recurrence and obviating stricture formation by scar tissue resulting from the defect in the common duct.

In summary, it may be stated that malignancies of the extrahepatic bile ducts should be treated by radical surgery when possible, even in the presence of local lymph node metastases, since excellent palliative results have been occasionally reported.

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RECURRENT VOLVULUS OF THE SIGMOID COLON

AN UNUSUAL CASE REPORT

DRURY HINTON, M.D., AND CHARLES A. STEINER, M.D.
PHILADELPHIA, PA.

ETIOLOGY.—Although volvulus of the sigmoid colon accounts for less than 1 per cent of acute intestinal obstructions, its high mortality of 30 to 45 per cent makes it surgically important. It is rare in young people, and somewhat more common in males, presumably due to a stronger abdominal wall and smaller pelvis.

The most important factor in the etiology of volvulus is a long mesentery with a narrow attachment to the posterior abdominal wall. The anatomy of the sigmoid, therefore, renders it more susceptible to twisting than any other part of the intestinal tract. Inflammatory adhesions may increase the narrowing of the mesenteric attachment.

Chronic constipation is a contributing cause of volvulus. The precipitating factor may be insignificant, such as change of position, exertion, or a purgative.

Once the twist has occurred, distention of the sigmoid, and later of the bowel above, develops as a result of putrefactive processes together with the obstruction. If the twist is complete with circulatory disturbance, rapid changes in the loop take place.

Symptoms.—In an actual acute attack, the chief symptoms are intermittent, colicky abdominal pain located near the obstruction, vomiting, constipation, and increasing distention of the abdomen. Tenderness and rigidity are rare. Temperature and pulse are normal. Peristalsis increases, and at times a mass may be felt in the left lower abdomen.

If unrelieved, the pain becomes more severe, but disappears with the onset of gangrene. Marked distention of the abdomen, tenderness and rigidity appear late, associated with necrosis of the bowel. In some instances the abdomen has a characteristic appearance, with distention at the sides and a groove in the center. Patients do not seem to become toxic as early with volvulus as with other types of acute intestinal obstruction.

Treatment.—If volvulus is suspected or diagnosed roentgenologically, before the actual acute attack takes place, it is sometimes possible to abort it. The treatment of acute volvulus is entirely surgical. Purgatives and enemata are useless. When possible, an effort should be made to learn the state of the patient's hydration and general condition, during which time parenteral fluids may be administered and some of the distention relieved by Wangensteen suction siphonage or a Miller-Abbott tube.

To facilitate the operation itself, spinal anesthesia is best. Through a left

paramedian incision, the involved loop is located, is untwisted, and a long rectal tube inserted into it manually through the rectum, to allow the passage of gas and liquid feces. The loop may first be aspirated to facilitate untwisting. Unless gangrene is present, this is all that is required to relieve the immediate condition. The rectal tube is allowed to remain.

Procedures have been recommended to prevent recurrent attacks of volvulus. Plication of the mesentery and fixation of the sigmoid to the parietal peritoneum or side-to-side anastomosis between the two limbs of the sigmoid loop are usually unsuccessful. If gangrene is present and resection is not feasible, the segment may be brought out upon the abdominal wall and excluded, as in a Mikulicz procedure, perhaps with a cecostomy in addition. The consensus is that some type of resection of the sigmoid is the method of choice if the patient will tolerate the procedure. In some instances of recurring volvulus, relief may be obtained by a rectal tube[1] passed into the sigmoid under direct vision through a large sigmoidoscope.

Case Report.—J. C., white, male, age 70, was first examined, March 14, 1934, following an attack of pain in the right lower quadrant. The diagnosis lay between acute intestinal obstruction and a right ureteral calculus, which had been passed. He was then well except for occasional slight pains and gradually increasing constipation until October 17, 1935, when he developed severe cramp-like abdominal pain and was unable to evacuate his bowels with laxatives, enemata, *etc.* He suffered with a distended abdomen, increasing pain, and nausea. He was admitted to the Delaware County Hospital, October 18, 1935.

Physical examination disclosed the abdomen to be markedly distended and tympanitic, and peristalsis was hyperactive, with moderate tenderness in both lower quadrants. During the next 48 hours little success was obtained in deflating his abdomen with the use of the Wangensteen suction and colonic irrigations. Meanwhile, with parenteral fluids his general condition somewhat improved. A roentgenogram showed the sigmoid and ascending colon to be greatly dilated, and the sigmoid unusually long and tortuous. Gas was present in the small intestine.

Upon operation, October 21, 1935, a large distended loop of sigmoid was found filling the center of the abdominal cavity. The junction of the sigmoid and rectum was encased in adhesions, and the sigmoid was twisted on itself, causing a volvulus. The distal bowel was collapsed. After freeing the adhesions and relieving the volvulus, a rectal tube was passed into the sigmoid through the anus. Passage of a large quantity of gas and liquid feces relieved the distention. The patient's condition was so grave that the operation was concluded at this stage. His postoperative course was uneventful, and he was discharged November 11, 1935.

For the next year and one-half he remained well, and controlled his constipation with mineral oil. On April 2, 1937, he was again unable to evacuate his bowels for several days, developed abdominal pain and distention as before, and was readmitted to the hospital. When enemata and colonic irrigations proved ineffectual, the patient was placed in the knee-chest position, a large sigmoidoscope was inserted, and a rectal tube passed through it by direct vision into the sigmoid. A considerable quantity of gas was expelled. The rectal tube was left in position for 48 hours, at which time the patient's abdomen was flat, and he was discharged.

Since then he has had five similar episodes, each of which was relieved in a similar manner, without hospital admission. Numerous minor attacks of distention without pain have in the interim been relieved by the assumption of the knee-chest posture at home.

SUMMARY

This case is presented to illustrate that there are occasional instances where chronic volvulus may be relieved by a nonsurgical procedure, which has been reported previously.[1] In desperate cases it can be considered as a substitute for operation or as a method of preparation of the patient until such time as he can stand surgical intervention. In our patient, relief has been so markedly effective that we have hesitated to recommend surgery in this case.

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MENINGOCELE SPINALIS TRAUMATICA SPURIA

WŁADYSŁAW DOBRZANIECKI, M.D.,
AND
EDMUND HAAK, M.D.
LWÓW, ROMANOWICZA-3, U.S.S.R.

FROM THE SURGICAL CLINIC OF LWÓW. DIRECTOR: PROFESSOR WŁADYSŁAW DOBRZANIECKI, LWÓW, ROMANOWICZA-3, U.S.S.R.

THE MOST FREQUENT complications in cases of fractures of the pelvis and the hip girdle are injuries to the kidneys, ureters, bladder, urethra and rectum. A particularly rare complication is injury to the spinal membranes, with passage of the cerebrospinal fluid into the soft tissues, which authors describe as "spurious posttraumatic meningeal hernia" *meningocele spinalis traumatica spuria.*

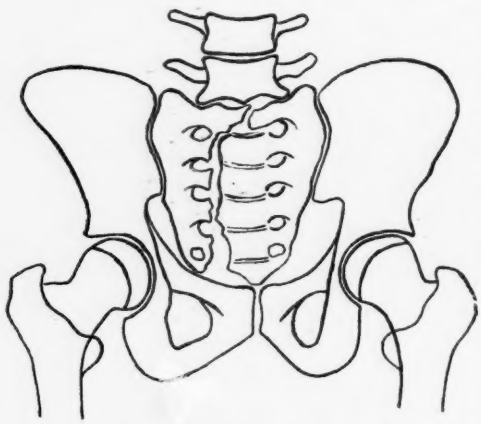

FIG. 1.—Diagram of the fracture based on the roentgenogram. This diagram shows distinctly the line of fracture of the first sacral vertebra, consequently running along the sacral orifices.

We have found in the literature only two references to such cases, similar in many clinical details to the case observed by us. In both instances, after trauma to the pelvis or the spine, the authors noted the appearance of a protuberance in the sacrolumbar region, containing a fluid which, after closer examination, was found to be identical with the cerebrospinal fluid.

In the case observed by Chodkow,[1] after a gunshot wound in the upper part of the spine, in a male, age 21, a paralysis of both lower extremities resulted, with loss of sensation to touch, retention of urine and feces, hematuria, and a protuberance in the sacro-iliac region. Compression of the tumor caused symptoms of increased intracranial pressure, such as headache, vertigo, nausea and bradycardia. In order to determine whether the liquid found in the tumor was connected with the subarachnoid space, a lumbar puncture was performed, and it was determined that the pressure was 125 Mm. Pressure exerted on the tumor caused a very marked increase of the pressure of the cerebrospinal fluid. Examination of the cerebrospinal fluid and of the fluid obtained from the tumor showed their identity both morphologically and chemically.

In the case reported by Schmidt,[2] a male, age 40, fell, and was injured in the coccygeal region. The roentgenogram showed a fracture of the fourth lumbar vertebra, and a tumor giving distinct signs of fluctuation was also

found. On the basis of these symptoms the author diagnosed an injury of the dura, with effusion of the cerebrospinal fluid through the laceration caused by the injury.

We shall describe our case somewhat more in detail, because of the great rarity of this type of fracture and also because of the application of myelography in determining the site of injury of the meningeal sac and its communication with the spurious hernia.

Case Report.—A male, age 26, fell from a tree, about ten meters high, striking the ground in a sitting posture, without losing consciousness after the accident.

He was taken home, where he remained three weeks without medical care and

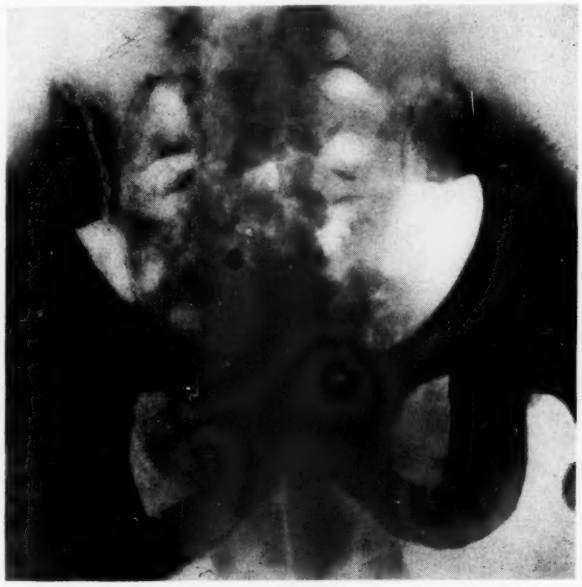

FIG. 2.—Exposure immediately after an intrathecal injection of 2 cc. of 40 per cent lipiodol, showing the passing of globules of lipiodol along the line of fracture of the sacral bone and gathering within the protuberance, descending into the intragluteal furrow.

without any therapy. He developed a severe headache, which continued for five weeks, although somewhat ameliorated.

After three weeks the patient tried to get up but could not stand on his feet. He did not notice any disturbance in urination, but complained, however, of constipation and pains during defecation, which he localized in the upper part of the rectum. The patient had a more severe headache when in the upright position, which he localized in the frontal region. He could not stand long. When standing, distinct fibrillations of the gluteal muscles, thigh, and the right leg could be seen. In attempting to walk he complained of pains in the right parasacral line. While walking he performed an adducting movement with the right extremity. The whole right limb showed muscular atrophy of a small degree, the right gluteal furrow was shallow, and somewhat lowered. The patient was able to maintain his equilibrium only by leaning on the right foot.

In the coccygeal region a protuberance could be seen, particularly on the right of the median line, about 13x11 cm. in size, descending low into the intragluteal furrow. The skin over the protuberance was somewhat stretched but otherwise unaltered. In the area of the protuberance distinct ballottement could be determined. Examination by

rectum revealed an elastic protuberance on the posterior wall, and the finger entered between two oblong fragments of the sacral bone.

Microscopic examination of the urine showed many white blood cells, phosphate crystals, and abundant bacteria. Spermatozoa were not found. Bacteriologic examination of the urine, both microscopic and on culture, showed *B. coli.*

FIG. 3.

FIG. 4.

FIG. 3.—Exposure nine days after the intrathecal injection of lipiodol. The lipiodol has formed three larger globules in the lower part of the protuberance.

FIG. 4.—Profile exposure showing the lipiodol gathering at the level of the last coccygeal vertebra and also beneath it.

Neurologic Status.—The cerebral nerves and the upper extremities showed no changes. The obdominal reflexes were, ambilaterally, present.

The lower extremities: The muscular tonus was, ambilaterally, normal. Adduction

of the right lower limb, both active and passive, was impossible because of pains in the region of the joint of the right hip. The motor power was normal. The knee and Achilles reflexes were present and equal. The muscles of the right thigh were sensitive to pressure, sensation was undisturbed, with the exception of a narrow band of hyperesthesia on the right buttock.

Chromocystoscopy showed no changes in the bladder, and no disturbances in the excretion of dyes.

Roentgenologic Examination.—This revealed a longitudinal fracture of the sacral bone on the right side. Otherwise the bones of the pelvis showed no changes (Fig. 1). A lumbar puncture and a puncture of the protuberance were performed. Both fluids were somewhat xanthochromic. The fluid obtained from the protuberance contained somewhat more albumin, probably due to stasis. Otherwise the two fluids, both morphologically and chemically, were identical.

After an injection of 2 cc. of 40 per cent lipiodol, a roentgenogram was immediately taken. Roentgenograms were also made two and nine days later, in the anteroposterior and lateral planes. It can be distinctly seen on the roentgenograms how small globules of lipiodol pass through the line of fracture of the first sacral vertebra, and then along the anterior orifices of the sacrum, that is, along the line of fracture of the sacral bone, and gather to form a more or less solid mass within the protuberance descending into the intragluteal furrow (Fig. 2). After nine days, the lipiodol was noted forming four larger globules in the lower part of the protuberance, and a profile roentgenogram showed the gathering of the lipiodol at the level of the last coccygeal vertebra and also beneath it (Figs. 3 and 4).

At the time of severe headaches, the patient was given sedatives and also strong hypertonic solutions intravenously to counteract edema in the central nervous system. The patient's condition improved very rapidly. Eight weeks after the accident he was able to walk quite normally, and has no other complaints, other than the headaches, which recur paroxysmally. The protuberance in the lumbar region diminished slowly; the skin over the protuberance, previously extended, can be made into a crease. Being of the opinion that the aperture in the dura would close spontaneously, the patient, after spending five weeks at the Clinic, was sent home, and was told to return after three months, for a follow-up examination. At that time, five months after the accident, the protuberance in the sacrococcygeal region had disappeared entirely, and the patient had returned to his usual work as a farmer, complaining only of some sensations in the right parasacral region at the site of the fracture.

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PERITONITIS DUE TO PERFORATION OF AN INFECTED URACHUS CYST

CASE REPORT

CLYDE EVERETT, M.D.

CLEVELAND, OHIO

FROM THE DIVISION OF SURGERY, CLEVELAND CITY HOSPITAL, CLEVELAND, OHIO

Case Report.—R. B., colored, male, age 39, was admitted to City Hospital, January 23, 1940, complaining of abdominal pain of three days' duration. The patient had been in good health until the onset of the present illness. The pain began in the suprapubic region and gradually became generalized over the whole lower abdomen. It was a dull aching type of pain. There was a mild dysuria associated with the onset of pain. Twelve hours before admission he developed nausea and vomiting, and from that time on the pain seemed to be more severe in the right lower quadrant. This persisted until the time of admission. Past history revealed that he had developed a urethral discharge three months before, which was due to a balanitis. This cleared up with treatment. There was no other history of gastro-intestinal or genito-urinary disturbances.

Physical Examination.—The patient was a well-developed and quite obese man, appearing acutely ill. Temperature 39°C. pulse 110, blood pressure 132/96. The abdomen was moderately distended. There was tenderness and muscle spasm over the whole lower abdomen, most marked in the right lower quadrant. There was marked rebound tenderness. No masses could be palpated. The genitalia were normal. Rectal examination showed marked tenderness of the pelvic peritoneum. White blood cell count 19,200; hemoglobin was 96 per cent. The urine showed albumin +, sugar ++++, acetone ++++, and a few pus cells. Blood sugar level 283 mg./100 cc., with a carbon dioxide combining power of 43 cc./100 cc. *Clinical Diagnosis:* Diabetes mellitus, with acidosis and peritonitis, probably due to appendicitis. Diabetic therapy was instituted, parenteral fluids were administered and the patient explored four hours later.

Operation.—Under spinal anesthesia, the peritoneal cavity was opened. Free pus was encountered. The appendix showed only a periappendical inflammation. A firm mass could be felt in the anterior abdominal wall, in the midline. It was extraperitoneal and just above the bladder. There was a perforation from the mass into the peritoneal cavity. In removing the mass, it was found to be firmly attached to the bladder, and to be attached to the umbilicus by a thin cord-like structure. The bladder was opened during this procedure; it was closed and the abdomen closed with drainage. The patient was quite sick for several days following operation, and the wound drained profusely. The diabetes was difficult to control during this time, but was easily controlled as the infectious process subsided. He was discharged on the nineteenth postoperative day.

Examination of the specimen showed acute and chronic inflammation, with sinus-tract formation. The cyst lining was almost completely destroyed by inflammation. No communication between the lumen of the cyst and the bladder could be found.

COMMENT.—Although this is a rare condition, nevertheless, it should be thought of in cases of peritonitis of obscure origin. In this case, the onset of pain in the suprapubic region and the accompanying dysuria gives a definite lead to the diagnosis. The physical signs, which may have been present early, were masked by the signs of peritonitis.

SPONTANEOUS AMPUTATION

ROBERT L. SEWELL, M.D.

ROCHESTER, N. Y.

FROM THE DEPARTMENT OF SURGERY, THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY, ROCHESTER, N. Y.

ORDINARILY, the onset of a gangrenous process anywhere in the body will, of itself, cause a person to seek medical aid. There are, certainly, very few localities in this country so isolated as to prevent a patient from obtaining help, if only from neighbors. That a woman living and working in a large city should tolerate a gangrenous foot for six months until it fell off, through sloughing, is almost incredible. Such a case, however, has recently been seen by us.

While arteriosclerotic gangrene of the toes, the foot, and even of the entire leg is not unusual, the uninterrupted process going on to a spontaneous amputation at the ankle is quite rare in this country.

Case Report.—R.M.H. No. 169826: K. A., female, age 74, employed as a housemaid in an old apartment house. On September 21, 1940, she was brought to the emergency department of the University of Rochester Hospital by the police. A gangrenous foot covered with small maggots, and of vile odor, was also brought wrapped up in an old newspaper.

With some difficulty her story was finally pieced together: She had had no previous trouble with her extremities aside from an injury to the right foot 12 years before. At this time she had dropped a heavy box filled with metal on the external aspect of the ankle. She was lame for several weeks, but had no further difficulty until December, 1939. She then noted that the entire right foot below the ankle would get cold and numb, and was frequently discolored when she had been out in the cold. Through the succeeding winter months the foot assumed a purple hue and steadily became darker. It, apparently, caused but little pain, as she continued working and refused to become upset about the change. By April, six months before being brought to the hospital, the foot had become "just like leather" from the ankle down. While she was unable to bear weight on it due to some discomfort, and due to instability at the junction with the normal tissue, she continued at her work around the apartment house. She spurned canes and crutches and got around by supporting herself on the back of a chair. She frequently used the affected foot to balance herself.

About one week before entry, she noticed that the gangrenous foot had become much looser, and that there were some breaks in the skin around the edges. Moderate swelling of both legs below the knees developed. For the first time she began to notice a disagreeable odor and the presence of maggots about the lesion. The part rapidly became looser, until the day before admission when it fell entirely away from the stump except for "several strings in the skin and one 'leader' the size of a pencil." As it was then impossible for her to put on shoes and stockings and go about her work, she called the janitor of the building and had him sever the few remaining connections with his razor. She then applied hydrogen peroxide to the stump. This was the only medication ever used except for some "liniment" she had applied to the part sporadically. The police were notified by another tenant in the building and they brought her to the hospital, where she was admitted despite her protests. She was rather indignant over the concern and interest which her condition elicited.

The past history revealed only the usual childhood diseases, moderate dyspnea on exertion for ten years, and nocturia for several years.

Physical Examination showed an elderly woman with definite senile cerebral changes. She was thin, weak, very pale and very dirty. Scabetic lesions, maggots, and lice were

FIG. 1.

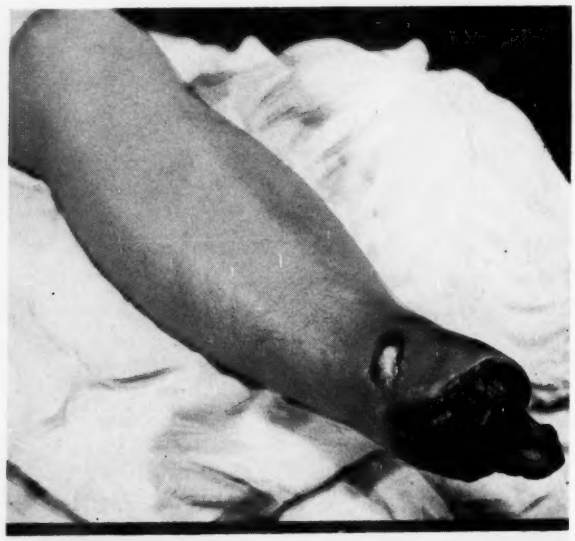

FIG. 2.

FIG. 1.—The granulating stump one week after admission. Note the ulcerated area on the anterior surface of the leg.
FIG. 2.—The gangrenous foot which was brought in with the patient.

thick on her body. The teeth were gone. The eye grounds showed retinal arteriosclerosis. The breasts were atrophic. There were many moist râles at the base of the right lung. The heart was slightly enlarged to the left and had an apical systolic murmur. The abdominal, pelvic and rectal examinations were normal. There were no glandular enlargements.

The stump of the right leg was for the most part covered by granulations. The ends of the tibia and fibula were partially eroded, but, as can be seen from the accompanying photograph (Fig. 1), the articular surface of the tibia was, in places, still intact. The end of the fibula extended only to a point 2 cm. above the end of the tibia. The granulations were quite redundant elsewhere, but of good color. There was a small, superficial, necrotic area in the skin 1 cm. in diameter, which lay about 3 cm. above the end of the stump.

Laboratory Data.—The most significant was the anemia. On admission, the R.B.C. 2.5 millions; W.B.C. 7,800; hemoglobin 7.0 Gm. Urine showed only 2 W.B.C. per high power field. She was given a small transfusion which brought her R.B.C. to 2.8 millions, and a second one bringing it to 3.17 millions. She was also given iron by mouth. Blood proteins were a trifle low—the albumin being 2.94 and the globulin 2.82. Chlorides were 604 milli-equivalents. The fasting blood sugar was 135 mg. per cent, and the glucose tolerance test was normal. Cholesterol was 163 mg. per cent, and the CO_2 combining power was 47.

Her hospital course was relatively uneventful. Twenty days after admission a supracondylar amputation was performed under spinal anesthesia. This height was selected because the vessels below the knee were shown to be inadequate by oscillometry. She ran a moderate fever for the first three postoperative days, and had some increase in the basilar râles. She was given hyperventilation and a short course of sulfathiazole; and her resulting stay was uncomplicated. The stump healed by first intention. On her eighth postoperative day she was given instructions in crutch walking. She remained quite sullen, and would not cooperate in the least in learning to walk, so was transferred to a county institution on her tenth postoperative day.

On May 29, 1942, the patient was still alive and performing part of her original duties at the apartment house. She refused all further medical attention. She is able to get around with the use of one crutch.

A review of the literature brings to light very few similar cases, though they, too, are frequently as bizarre as this. One famous case was that of Rooker,[1] which occurred in a 14-year-old boy who had a fracture of both bones of the proximal portion of the forearm. While under observation, gangrene of the entire right arm up to the shoulder girdle developed. Sloughing at this joint eventually occurred spontaneously, with the formation of a satisfactory stump.

Often, in children, spontaneous amputation occurs after the onset of a "spontaneous gangrene." This, in turn, has usually followed an infectious process elsewhere in the body. Frequent forerunners of spontaneous gangrene are tuberculosis, diphtheria, less often scarlet fever and rheumatic fever. A careful analysis of these[2] has established the fact that the gangrene may be due to embolism, autochthonous thrombosis, or even to an endarteritis in which spasm of the vessels is prominent. Often several areas are similarly involved.

In adults, one of the chief causes of spontaneous amputation is thromboangiitis obliterans, although usually only the phalanges are involved. However, several years ago we saw a middle-aged male with Buerger's disease with gangrene of the whole foot except for the heel. As there was no infection and no break in the skin surface he was followed conservatively in the hospital for five weeks until sloughing started. The process was then interrupted by removing the foot. This was accomplished very simply by cutting

through the joint capsule of the ankle and dissecting off the intact skin of the heel, and folding it anteriorly to cover the end of the stump. This end-result was entirely satisfactory. It is unwise, in Buerger's disease, to amputate the leg when the gangrene involves only the foot and not the heel.[3]

Even more exceptional than in Buerger's disease is the occurrence of spontaneous amputation due to arteriosclerotic changes. While frequent losses of toes and fingers are cited, there is no previous report of a case in which a major spontaneous amputation has taken place, although this eventuality is frequently suggested.

The more customary, and far from unusual, course of events in arteriosclerotic disease is for amputation to be performed before actual sloughing of the gangrenous areas has started. Then, too, if spontaneous amputation is to occur, the demarcation must be right at a joint. Otherwise the bone will prevent loss of the part until it is eroded through by chronic infection.

The progression of such a case of arteriosclerotic gangrene could scarcely occur in a person with other than the peculiar phlegmatic make-up which this patient presented. Indeed it was only against her wishes that she was brought to the hospital after the foot was off.

Several factors evidently prevented the onset of acute difficulties earlier. Paramount, perhaps, was the fact that she maintained an intact skin surface up until the last several weeks. Otherwise the onset of an infection would have precipitated some action on her part, or would have called the attention of others to her earlier. Secondly, after the skin break occurred with inevitable infection plus the large amount of necrosis, it is likely that the maggots were beneficial in cleaning away the dead tissue connected to the granulating stump. Even when she first came into the hospital the granulations were healthy. A third significant factor in her case, which permitted the spontaneous amputation, or rather the disarticulation, to go on, was that the demarcation took place just at the junction of the astragalus with the tibia and fibula.

SUMMARY

A case of spontaneous amputation of the entire foot is cited in a 74-year-old woman. The underlying disease was arteriosclerosis; and the time necessary for the process was about six months.

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SIPHON DRAINAGE FOR SUPRAPUBIC CYSTOSTOMY

O. A. NELSON, M.D.
SEATTLE, WASH.

DURING the last 18 months we have used for patients with suprapubic cystostomy a siphon drain which has worked so well that rarely has the urine soiled the dressings. Consequently, excoriation of the skin and malodor from decomposing urine are prevented. Such a condition makes the convalescing period more pleasant for the patient, and attended by less suffering than when he is soaked in urine.

The use of the siphon also seems to promote healing of the incision, and to clear up the bladder infection much earlier than when the stagnated urine is allowed to remain in the bladder. Furthermore, nursing care and dressing expenses are very greatly reduced. In fact, the suprapubic incision is dressed only every day or two. In no instance have we seen irritation to the bladder, or any other harm, come from the use of this apparatus.

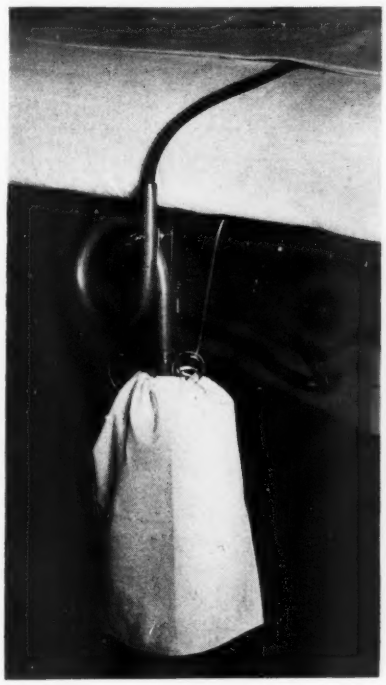

FIG. 1.—Siphon showing metal coil fixed in position on bed.

The employment of a siphon for bladder drainage is not new It was described by Chiene,[1] in 1876, and by Boyd,[2] in 1936. During the last 25 years we also have tried to use a siphon drain with a fluid trap, but the drainage was not satisfactory until we splinted the part of the tubing forming the trap with a metal coil, and used a large catheter and large rubber tubing.

The apparatus consists of:

(1) A soft-bulb Pezzar Catheter Nos. 30 F. or 32 F. (Bard, Inc., of New York make a catheter excellent for this purpose.)

(2) A rubber tube seven feet long, of 3/8-inch diameter, the wall of which should be 3/32-inch.

(3) A metal coil at least six inches in diameter on the inside, to go over the rubber tubing.

(4) A large glass connection to connect the catheter to the rubber tubing.

The siphon is set up as follows:

After the above articles are sterilized, the Pezzar catheter is placed just

inside the bladder. The rubber tubing is filled with sterile water, and all air expelled. The rubber tubing is connected to the catheter, and the metal coil passed over the distal end of the tubing. Then the coil is placed some inches below the bladder (preferable arrangement is to clamp it on the bedrail). Care must be taken not to place the coil too low, so as to cause too great suction, and pain to the patient. Care must also be exercised not to allow air to be sucked into the drainage system at the bladder or connection. It is well to tie both the catheter and the tubing on to the glass connection. If there is formation of urinary precipitate, the tube should be irrigated every day or two; but mucus or pus does not clog the drainage system.

After suprapubic prostatectomy, we use the siphon as follows:

The suprapubic drain is left in place until the urine has been entirely clear for several days. Then a No. 22 F., three-eyed, open-end catheter is placed through the urethra, and the siphon system attached to the catheter. To hasten the healing of the suprapubic fistula, the bladder is distended once a day by injecting fluid through the catheter. After the bladder has been healed four or five days, the catheter is removed.

Practically all of these patients leave the hospital, with the suprapubic incision healed, in from 16 to 20 days after the enucleation of the gland.

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[1] Chiene, J.: New Method of Wound Drainage. Edinburgh Med. Jour., **22**, 224–229, 1876.

[2] Boyd, Montague L.: Suprapubic Cystotomy for Drainage. Jour. Urol., **36**, 740–755, December, 1936.

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Walter Estell Lee, M.D.
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